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Patterns of Care in Patients with Pancreatic Cancer

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Abstract

Background

Pancreatic cancer has the lowest survival rate of all cancers in Australia, with an estimated five-year relative survival of 6%. Screening for early pancreatic cancer is currently not feasible and at present there are no new systemic treatment regimens on the horizon that will radically alter prognosis. Therefore, in the short-term, the largest improvements in patients' outcomes will be gained through ensuring that all patients receive optimal (or best-practice) care.

International evidence suggests that some evidence-based treatments for pancreatic cancer are under-utilised and that there is inequitable access to high-quality care. In Australia, there is very little current population-based information on the types of care that patients with pancreatic cancer receive, nor the factors that influence the care provided. Given Australia's unique geography and health-system, local information is required to understand patterns-of-care for patients with pancreatic cancer as well as the sociodemographic and health-service factors associated with receipt of optimal care in this country.

Aims

The aims of this work were to:

1. Identify indicators of care that clinicians believe important in the management of patients with pancreatic cancer
2. Describe the proportions of pancreatic cancer patients who receive different treatment modalities.
3. Identify determinants of variability in delivery of cancer-directed therapies.
4. Determine if patient, tumour or health service factors influence survival of patients with non-metastatic disease.
5. Develop a quality-of-care score based on the indicators of care identified by clinicians and (a) investigate factors associated with the quality-of-care score; and (b) examine the association between the quality-of-care score and overall survival.

Methods

The research described in this thesis was nested within a population-based study of patterns of care for Australian patients with pancreatic cancer. The study was a retrospective comprehensive medical record review of all patients diagnosed with pancreatic cancer in Queensland (QLD) and New South Wales (NSW) between July 2009 and December 2010 (NSW) or June 2011 (QLD).

We used a Delphi process with a range of clinical specialists to identify indicators of optimal care. We applied the mean score of importance to the clinical data to calculate a quality-of-care score for patients in the patterns-of-care study.

Data from the patterns-of-care study were also used to describe management and treatment patterns, and survival outcomes. Factors related to the quality-of-care score and receipt of surgery were investigated.

Statistical analyses included multivariable logistic regression, Kaplan-Meier methods to construct survival curves and estimate survival times, and Cox proportional hazards models.

Results

The NSW and QLD cancer registries identified 2090 patients as potentially eligible for inclusion in the patterns-of-care study cohort. Records were reviewed for 2003 (96%) patients and 140 (7%) of these were found to be ineligible for the study. The median age of the 1863 eligible patients was 72 years, 54% were men and over half had metastatic disease at diagnosis.

The Delphi process included responses from 63 participants (66% of those sent the final questionnaire; 25% of those initially invited). Specialties of the participants invited included surgery, medical oncology, allied health and nursing, gastroenterology, palliative care, radiation oncology, interventional radiology, general practice, gerontology and medicine. Consensus was reached for many items, such as the need for patients to be assessed by a hepatobiliary surgeon, for surgery to occur in a high-volume centre and the importance of management by a multidisciplinary team, but there was some variability according to the specialty of the clinician. Surgeons tended to prioritise surgical factors and, compared with other clinicians, considered supportive care less important.

Among the patients in the patterns-of-care study, the median survival was 4.5 months and 22% were alive at least one year after diagnosis. Consistent with the international literature, approximately 15% of patients underwent resection of their primary tumour and three quarters of these received adjuvant chemotherapy. Less than half of the patients were reviewed by a multidisciplinary team, and only 51% of patients who did not have metastatic disease were reviewed by a specialist hepatobiliary surgeon.

Age, comorbidities, tumour stage and increasing remoteness of residence were significantly associated with poorer survival in patients without metastatic disease at diagnosis. This is likely to have been at least partially influenced by access to surgery, with patients from rural areas being less likely to be offered resection of their tumour than those living in cities.

For the quality-of-care scores derived from the Delphi process, the scores for patients living in rural or more socio-economically disadvantaged areas were statistically significantly lower than for patients living in major cities or least disadvantaged areas. Quality-of-care scores were higher for patients who were younger, with better performance status, or who first presented to a hospital with a high pancreatic-cancer-case volume. Higher scores were associated with better survival.

Conclusions

This research emphasised the importance of highly expert care in the management of patients with pancreatic cancer, but found that care was highly variable and dependent on a range of factors, including region of residence. Implementing strategies to ensure equitable access to optimal care for all patients diagnosed with pancreatic cancer, may improve outcomes for people diagnosed with this devastating disease.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

I acknowledge that an electronic copy of my thesis must be lodged with the University Library and, subject to the policy and procedures of The University of Queensland, the thesis be made available for research and study in accordance with the Copyright Act 1968 unless a period of embargo has been approved by the Dean of the Graduate School.

I acknowledge that copyright of all material contained in my thesis resides with the copyright holder(s) of that material. Where appropriate I have obtained copyright permission from the copyright holder to reproduce material in this thesis.

Publications during candidature

Peer-reviewed publications:

1. **Burmeister EA**, O'Connell DL, Jordan SJ, Goldstein D, Merrett ND, Wyld D, Beesley VL, Gooden HG, Janda M, Neale RE. Factors associated with quality of care in patients with pancreatic cancer. MJA 2016; 205(10):459-465.
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3. **Burmeister EA**, Jordan SJ, O'Connell DL, Goldstein D, Merrett ND, Wyld D, Beesley VL, Gooden HG, Janda M, Neale RE. *Determinants of survival and attempted resection in patients with non-metastatic pancreatic cancer: an Australian population-based study*. Pancreatology 2016; 16 (5): 873-81.
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Book chapter:

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2. **Burmeister EA**, Jordan SJ, O'Connell DL, Beesley VL, Goldstein D, Gooden HM, Janda M, Merrett ND, Wyld D, Neale RE. *Determinants of attempted resection for patients with non-metastatic pancreatic cancer*. June 2015, European Pancreatic Club Meeting, Toledos Spain.
3. Neale RE, Waterhouse M, **Burmeister EA**, O'Connell DL, Beesley VL, Goldstein D, Gooden HM, Janda M, Jordan SJ, Merrett ND, Payne ME, Wyld D. *Determinants of outcomes following resection for pancreatic cancer- An Australian population-based study*. June 2015, European Pancreatic Club Meeting, Toledos, Spain.
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Publications included in this thesis

Included in this thesis are 6 publications: three published papers; one paper accepted for publication, as results chapters and two associated publications included as appendices. Publications included in the thesis are as follows:

1. **Incorporated as Chapter 4:**

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Contributor	**Statement of contribution**
Author **EAB** (candidate)	Study conception and design (42%) Data collection (100%) Data cleaning (90%) Data analysis (80%) Interpreted results (40%) Wrote paper (75%) Edited paper (36%) Submitted and revised paper (90%)
Author SJJ	Study design (2%) Interpreted results (10%) Wrote and edited paper (10%)
Author DLO	Study conception and design (12%) Interpreted results (4%) Wrote and edited paper (2%)

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Author HMG	Study conception and design (2%) Edited paper (2%)
Author MJ	Study conception and design (2%) Edited paper (2%)
Author NDM	Study conception and design (2%) Interpreted results (2%) Wrote and edited paper (2%)
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- Panelists for the quality-of-care score Delphi process: The pancreatic cancer study group (Appendix B).

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pancreatic cancer, patterns of care, quality of care, process of care, health services, care score, determinants of care, survival.

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List of Abbreviations used in the thesis

AHR	Adjusted Hazard Ratio
AJCC	American Joint Committee on Cancer
AOR	Adjusted Odds Ratio
ARIA	Accessibility/Remoteness Index of Australia
ASR (w)	Age-Standardised Ratio/rate (world population)
CA 19-9	Carbohydrate Antigen 19-9
CI	Confidence Interval
CRF	Case Report Form
CT	Computerised Tomography
CV	Coefficient of Variation
ECOG	European Cooperative Oncology Group (performance status)
ERCP	Endoscopic Retrograde Cholangiopancreatography
ESDO	European Society for Digestive Oncology
ESMO	European Society of Medical Oncology
EUS	Endoscopic Ultrasound
FNA	Fine Needle Aspiration
GP	General Practitioner
HPB	Hepatobiliary
HR	Hazard Ratio
IMRT	Intensity Modulated Radiation Therapy
IRSD	Index of Relative Socio-economic Disadvantage
LGA	Local Government Area
MDT	Multidisciplinary team
MRCP	Magnetic Resonance Cholangiopancreatogram
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Database
NCICCC	National Cancer Institute designed Comprehensive Cancer Centre
NSW	New South Wales
OR	Odds Ratio
PBS	Pharmaceutical Benefits Scheme
PET	Positron Emission Tomography
PSC	Pancreatic Stellate Cells
PTC	Percutaneous Transhepatic Cholangiogram
QLD	Queensland
QOL	Quality of life
R0	Margins clear of tumour following resection
R1	Microscopic disease remaining in tumour bed following resection

R2	Macroscopic disease remaining following resection
SEER	Surveillance, Epidemiology and End Results program
SEIFA	Socio-Economic Index For Areas
SES	Socio-Economic Status
SLA	Statistical Local Area
TNM	Tumour, Nodal, Metastases (staging)
UICC	International Union Against Cancer
UK	United Kingdom
USA	United States of America
VMAT	Volumetric-modulated arc therapy

Chapter 1: Background and literature review

1.1. INTRODUCTION

In developed nations pancreatic cancer is the 10th most common cancer.[1] However it has the worst survival of any cancer type so it is the 5th most common cause of cancer death in men and the 4th most common in women. Current statistics suggest that one out of every 72 people in Australia is likely to die from pancreatic cancer before the age of 85- a total of about 2800 deaths per year.[2]

Currently the only potentially curative treatment is resection of the pancreatic lesion. Patients who undergo a completed resection have five-year survival of approximately 15-20% compared to less than 5% for the 80% of patients who are diagnosed at a stage when resection is not possible due to invasion of nearby blood vessels or the presence of distant metastases. There are a variety of chemo- or radio-therapeutic options available for use in either adjuvant or palliative settings. These treatments provide only modest survival gains but can offer improvements in quality of life.[3]

Ensuring best practice care for all patients may lead to improvements in survival and/or quality of life. Recommendations regarding diagnosis, staging and treatment of pancreatic cancer arose from the World Congress on Gastrointestinal Cancer (Barcelona 2006)[4] in 2006, and a 2012 meeting led to additional recommendations for management of metastatic cancer.[5] The United States National Comprehensive Cancer Network (NCCN)[6] has also published guidelines. Despite these publications there is evidence from a range of countries that there is variability in management and under-use of treatment for patients diagnosed with pancreatic cancer.[7-9] Rurality of residence, socio-economic status, marital status and age have all been shown to influence the treatment and management of care that patients receive.[10-13]

In Australia there appears to be variability in survival according to location of residence, with people living in rural areas having poorer survival than those in cities.[14, 15] The reasons for survival disparities are unclear, although differences in access to treatment have been suggested.[16, 17]

There have been few attempts to describe management of pancreatic cancer in Australia. A population-based study in Victoria described under-utilisation of treatments but, apart from examining the association with age, they did not explore patient or health system factors that might influence treatment decisions.[18] In addition, the situation may have changed in the decade since the data for that study were collected and patterns observed in Victoria, a small and relatively urbanised state, may not be generalisable to other states. Describing patterns of care is important to identify avenues for ensuring that all patients receive optimal care.[19]

This literature review provides background information pertinent to my doctoral research project. It includes information regarding the anatomy and function of the pancreas and the epidemiology of

pancreatic cancer. It then describes risk factors and symptoms of pancreatic cancer and approaches to management including diagnosis, staging and treatment. Patterns-of-care studies are reviewed including the methods used, the quality of the studies and the key results found. The variations in receipt and quality of care are described, as are the determinants of access and the relationships between management and care received and patients' outcomes.

1.2. OVERVIEW OF THE THESIS

This thesis entitled "Patterns of care in patients with pancreatic cancer" includes a review of current literature; methods; three published manuscripts and one accepted manuscript as results chapters; followed by a discussion and conclusion of the findings of this research.

Chapter 1 includes an appraisal of the literature associated with the research aims, with a focus on the epidemiology of pancreatic cancer, optimal care for patients with pancreatic cancer, current patterns of care and factors associated with care and management, both in Australia and Internationally.

Chapter 2 states the aims and hypotheses of the research.

Chapter 3 provides an overview of the methods and includes a description of my contribution to the research. Further details, particularly of analytical methods, are shown in the methods section of each published manuscript.

The results are presented in Chapters 4 to 7 (all published or in press manuscripts).

Chapter 4 identifies factors of care that pancreatic cancer clinicians identified as important in the care of patients with pancreatic cancer. This was completed using a Delphi process which enabled each factor to be quantified. The factors and scores are presented in a published manuscript.

Chapter 5 includes a publication which presents an overview of patterns of care for patients with pancreatic cancer in NSW and QLD.

Chapter 6 presents mortality and survival rates for patients diagnosed with non-metastatic disease and factors associated with 1) survival; 2) determinants of classification as potentially resectable; and 3) determinants of attempted resection.

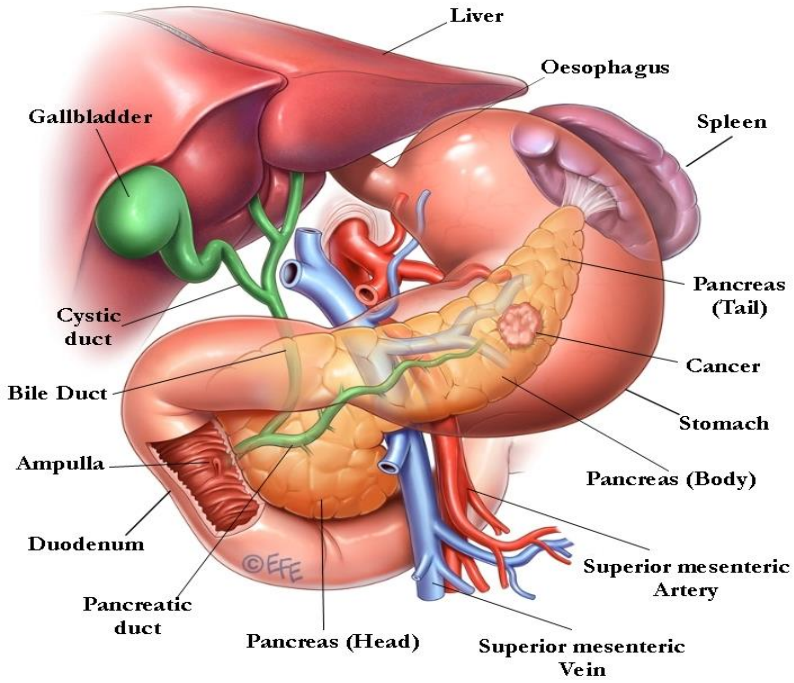
Chapter 7 shows the development of an overall quality-of-care score based on the factors identified during the Delphi process. Factors associated with the score and the association of the score with survival are presented.

Chapter 8: offers a comprehensive discussion of the research, including an overview of the significant findings, how the findings relate to other recently published literature and the strengths and limitations of the research. The implications of the results, including future issues to be considered to improve outcomes for patients diagnosed with pancreatic cancer are also discussed, followed by a conclusion.

Literature review

1.3. ANATOMY AND FUNCTION OF THE PANCREAS

The pancreas lies across the back and centre of the abdomen behind the stomach and close to the kidneys, spleen and liver. It is a long tapered organ with the widest part (the head) near the duodenum, extending through the body to the tail, which is situated near the spleen. It is surrounded by major arteries and veins as shown in Figure 1-1.[20]



Source: The Pancare Foundation[20]

Figure 1-1: Anatomy of the pancreas in the abdomen

The pancreas is a glandular organ, vital to metabolism, made up of two types of glands: exocrine glands which secrete digestive enzymes used by the body to break down fats, proteins and carbohydrates; and endocrine glands that secrete hormones, most notably insulin and glucagon, which regulate blood glucose levels.

1.4. PANCREATIC CANCER CHARACTERISTICS

Almost 95% of all pancreatic cancers arise in pancreatic exocrine tissue and are classified as exocrine tumours, usually invasive ductal adenocarcinomas. Other pancreatic cancers include slower-growing neuroendocrine tumours, rarer acinar cell carcinomas which are associated with the

release of digestive enzymes into the bloodstream, and low-grade solid-pseudopapillary neoplasms which mainly arise in young women.[21] About 75% of pancreatic cancers arise in the head of the pancreas, 15-20% in the body and 5-10% in the tail of the pancreas.[22] The most frequent site of metastases from pancreatic adenocarcinomas is the liver (~75%), but spread to the peritoneum, lymph nodes, bone, lung and pleura also occurs.[23]

The focus of this thesis will be on pancreatic adenocarcinoma. The term pancreatic cancer from here-on will refer to pancreatic adenocarcinoma unless otherwise stated.

1.5. BIOLOGY OF PANCREATIC CANCER

Pancreatic cancer is genetically highly heterogeneous, but mutations in a number of key driver genes have been identified.[24] The most common of these are activating mutations in the KRAS oncogene, which is mutated in over 90% of all pancreatic cancers. Inactivating mutations in three tumour suppressor genes (CDKN2A, TP53, SMAD4) have been identified in over 30% of all pancreatic cancers.[25] In addition to these genes there are many more that are mutated at low frequency, some of which will also be driver genes.

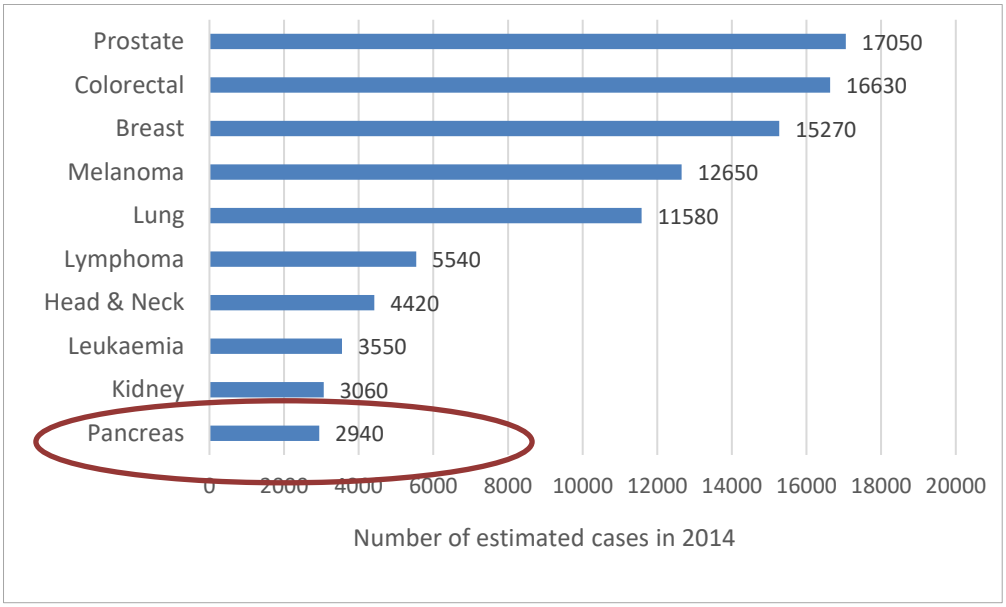
The most widely accepted model of pancreatic carcinogenesis is that the tumour originates in well-defined precursor lesions called pancreatic intra-epithelial neoplasms (PanINs). These progress from low-grade PanIN-1A lesions through to high-grade Pan-IN-3 lesions over a period of at least 10 years.[26] KRAS appears to be the earliest mutation, with other genes becoming mutated during the progression to neoplasia. After the founder cell is originated it takes approximately a further five years for the development of metastatic potential.[27] Thus, a long window exists during which early detection could potentially reduce the risk of metastatic pancreatic cancer.[21]

Pancreatic cancer is characterised by the presence of dense collagenous stromal tissue. The stroma contains a variety of cells, including pancreatic stellate cells (PSCs). There is a complex interplay between PSCs and pancreatic cancer cells.[28] Pancreatic cancer cells release chemokines that recruit PSCs to their vicinity and promote their activation. The PSCs then participate in pancreatic cancer progression by stimulating proliferation, inhibiting apoptosis and promoting cancer cell migration.[29] This, along with the challenges of drug delivery through the dense surrounding tissue, is thought to contribute to the highly aggressive nature of pancreatic cancer. However, two recent studies have suggested that the stroma may actually protect against progression, raising the possibility that the role of PSCs may be context dependent.[30, 31]

1.6. EPIDEMIOLOGY OF PANCREATIC CANCER

1.6.1. Incidence

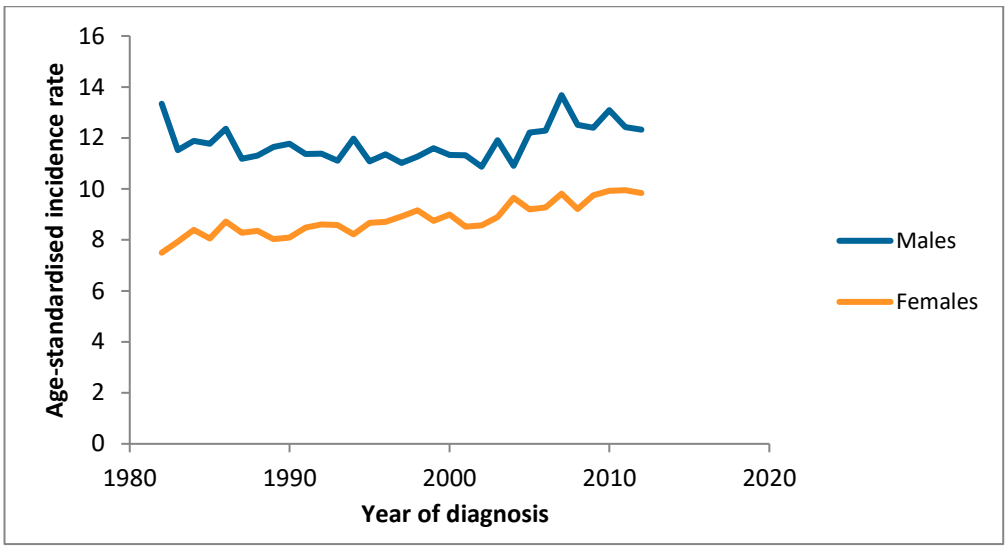
Pancreatic cancer is the 10th most commonly diagnosed cancer in Australia (Figure 1-2).[32] Current statistics estimate that one out of every 65 people are likely to develop the disease before the age of 85 years.[2] The age-standardised incidence rate is 6.6 per 100,000. This is consistent with figures from other more developed countries in the world.[1]



Source: Australian Institute of Health and Welfare[32]

Figure 1-2: The estimated 10 most commonly diagnosed cancers, Australia, 2014

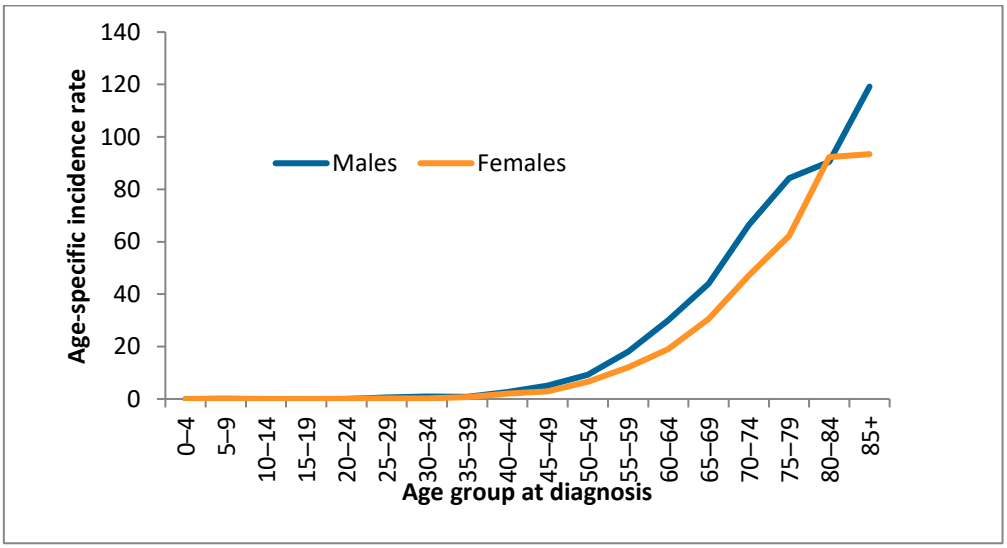
The incidence of pancreatic tumours has been gradually rising in Australia, particularly in women, with an age-standardised incidence rate per 100,000 population of 7.5 in 1980, rising to 9.8 in 2012 (Figure 1-3).[32]



Source: Australian Institute of Health and Welfare[32] (Age-standardised to the 2001 Australian standard population)

Figure 1-3: Australian age-standardised (per 100,000 population in Australia 2012) incidence rate of pancreatic cancer by year

Pancreatic cancer is predominantly a disease of older age. The median age at diagnosis is about 70 years and it is rarely diagnosed in patients under the age of 40 years (Figure 1-4).[2, 33]



Source: Australian Institute of Health and Welfare[32, 34]

Figure 1-4: Age-specific incidence rate by age group, for 2012

Developed regions of the world have a much higher age-standardised incidence rate of pancreatic cancer than less developed regions (7.2 and 2.8 per 100,000 population respectively) (Figure 1-5).[1] It is likely that this is at least partly related to differences in diagnosis and cancer registration.

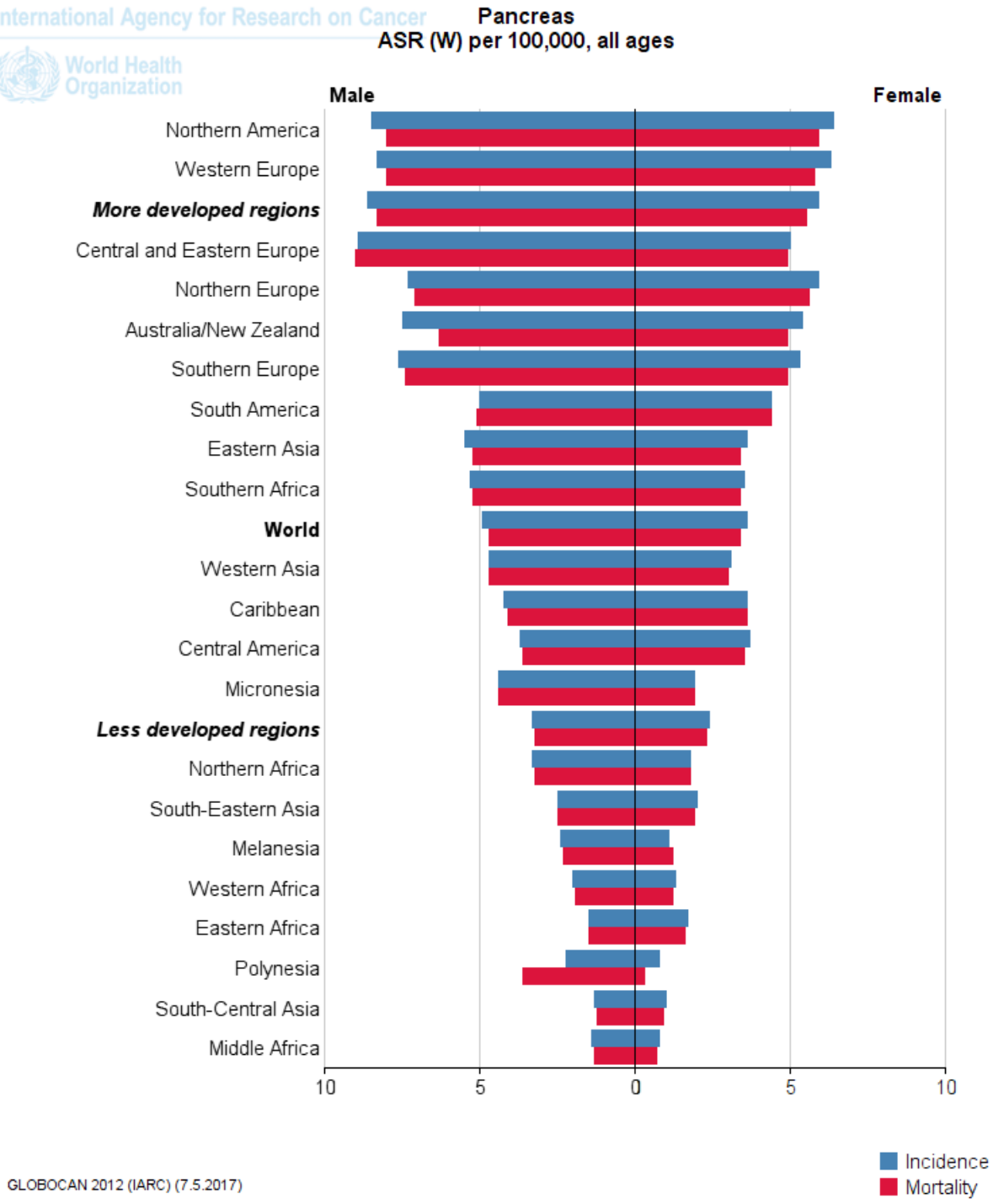


Figure 1-5: World Areas, estimated age-standardised (per 100,000 world population 2012) Incidence and Mortality rates of pancreatic cancer by gender.

1.6.2. Mortality and Survival

People diagnosed with pancreatic cancer have the poorest prognosis compared with people diagnosed with any other cancer and it is thus the fourth leading cause of cancer-related death in Australia.[35] One-year overall survival is currently 20%, and 6% of patients survive five years following diagnosis, which mirrors survival estimates from other western countries.[32, 36, 37] Despite some modest improvement in five-year relative survival (Figure 1-6),[38, 39,] unlike some cancers that have experienced dramatic recent reductions in mortality rates such as breast and colorectal cancers,[35] current projections suggest that pancreatic cancer will be the second leading cause of cancer death in the United States (USA) before the year 2030.[40]

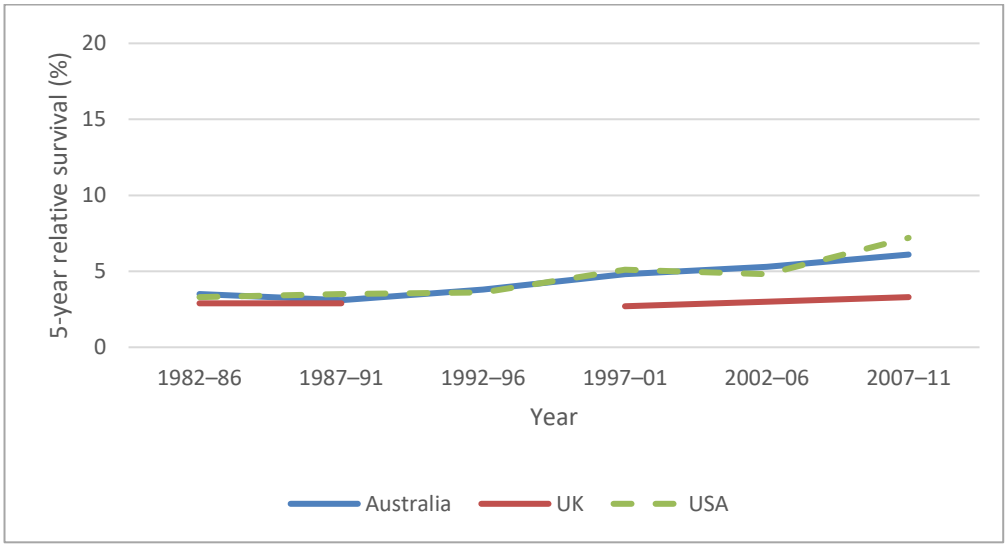


Figure created with data sourced from references[32, 34, 39] UK: United Kingdom; USA: United States America

Figure 1-6: Five-year relative survival over time in Australia, United Kingdom and United States

1.7. RISK FACTORS ASSOCIATED WITH PANCREATIC CANCER

A number of factors have been consistently associated with risk of pancreatic cancer. These include:

- Cigarette smoking: Current smokers are almost twice as likely to develop pancreatic cancer as non-smokers.[41, 42] It has been estimated that 23% of pancreatic cancers diagnosed in Australia have cigarette smoking as a contributing risk factor.[43]

- Obesity: People with a body mass index of > 25kg/m^2 have a 25% increase in risk of pancreatic cancer compared to those ≤ 25 kg/m^2,[42, 44] and for each 5-unit increase in body mass index there is a 10% increase in risk.[45] Approximately 8% of pancreatic cancers in Australia are attributable to being overweight or obese.[46]
- Alcohol consumption: Heavy alcohol consumption (three or more alcoholic drinks per day) compared to low consumption increases the risk of pancreatic cancer by about 40%.[42, 47] More modest alcohol intake does not appear to influence the risk of developing pancreatic cancer.
- Race: More African Americans develop pancreatic cancer than white Americans but this increased risk may be due to differences in smoking status or other lifestyle factors.[48]
- Diabetes: Long-standing diabetes increases the risk of pancreatic cancer. Onset of diabetes within 2-8 years prior to study entry has been associated with an 80% increase in the risk of pancreatic cancer.[49, 50] Patients with diabetes and chronic pancreatitis are more than twice as likely to develop pancreatic cancer as diabetics without chronic pancreatitis.[51]
- Genetic factors: Approximately 10% of pancreatic cancer cases occur in high-risk families. Known genetic syndromes, such as Peutz-Jeghers account for a small proportion of these, with the underlying mutations unknown for a high proportion of familial cases. The standardized incidence ratio can be as large as 17 for people with three or more first-degree relatives who developed pancreatic cancer.[52-54]
- Diet: The role of diet in risk of pancreatic cancer is not entirely clear although there is some evidence that fruit consumption can reduce risk [42] and consumption of red meat and nitrosamines can increase risk.[55]

1.8. SYMPTOMS OF PANCREATIC CANCER

Symptoms of pancreatic cancer are often non-specific and this possibly contributes to the late stage of presentation. Symptoms can include vague abdominal discomfort, nausea, anorexia, weight loss, changed bowel habits, fatigue and lethargy. There are some more specific symptoms including jaundice, epigastric pain, diabetes and pancreatitis and it is often these that will trigger clinical presentation.

Jaundice: If the tumour arises in the head of the pancreas the common bile duct is often blocked causing increased levels of bilirubin in the blood. This in turn leads to jaundice (yellow pigmentation of the skin and eyes), dark urine and pruritus (itchy skin). Jaundice occurs in up to

70% of patients with cancer of the head of the pancreas,[56] but is less frequent if the tumour occurs more distally.

Epigastric pain: The coeliac plexus is a group of nerves very close to the pancreas, and as the disease spreads patients are often troubled by severe pain due to involvement of these nerves. This pain is usually described as epigastric pain but often radiates through to the back and shoulder, particularly if the liver is involved.

Diabetes: Diabetes or hyperglycaemia is found in up to 85% of patients diagnosed with pancreatic cancer.[57] It has been suggested that newly diagnosed diabetes could be indicative of a pancreatic cancer diagnosis.[58] Recognition of newly diagnosed diabetes as an early manifestation of pancreatic cancer could be exploited as a screening tool, although this may be unfeasible due to the large number of people diagnosed with diabetes and the relatively rare diagnosis of pancreatic cancer.[59]

Pancreatitis: Occasionally pancreatic cancer can also cause acute pancreatitis[60] which is characterised by severe abdominal pain.[61]

1.9. CLINICAL MANAGEMENT OF PATIENTS WITH PANCREATIC CANCER

1.9.1. Diagnosis and staging of pancreatic cancer

Accurate diagnosis and staging in patients with a differential diagnosis of pancreatic cancer is difficult due to the anatomic location of the pancreas. Recent developments in medical imaging have made diagnosis and staging less complex, but these investigations often require specialised equipment and expertise.[62] There are various investigations that can be used to assist diagnostic confirmation and staging of the disease.

Computed tomography (CT): Non-contrast CT scans have poor sensitivity and specificity for pancreatic cancers and evaluation of the extent of tumours, thus are only recommended for patients unable to tolerate iodine contrasts.[63] However, a multiphase CT scan with contrast provides high image resolution and information on tumour extent, organ and vascular involvement, lymph node and hepatic metastases. It is the primary method for evaluating resectability,[60] and is able to predict surgical resectability with about 85% accuracy.[58] It is generally accepted that the optimal test for diagnosis and staging is a contrast-enhanced CT scan[64] and that expertise in interpreting these pancreas-protocol scans in high-volume specialist centres improves staging accuracy and management in patients with pancreatic cancer.[65]

Endoscopic ultrasound (EUS) and endoscopic retrograde cholangio-pancreatography (ERCP) are used to assess the tumour, vascular invasion (particularly the portal and splenic vein), tissue diagnosis, lymph node disease (reliably identifying disease in coeliac and mediastinal nodes), small volume liver disease, peritoneal ascites and to visualize the pancreatic ducts, all of which help to ascertain the resectability of the tumour. If a mass is observed during the EUS a fine needle aspiration (FNA) is performed with the sensitivity for diagnosing pancreatic cancer by EUS-FNA being approximately 85%.[66] The main limitation of EUS is its functional dependence on the expertise of a gastroenterologist, but with the increasing use and accuracy of pancreas-protocol CTs to assess resectability, the need for EUS is declining.[63] ERCP is predominately used for palliation of biliary obstruction and has a limited role in defining resectability of the tumour.[63]

Magnetic resonance imaging (MRI) [and magnetic resonance cholangiopancreatogram (MRCP)] enables clinicians to investigate the extent of the pancreatic tumour and the biliary and pancreatic ducts in patients who have equivocal findings following a pancreas-protocol contrast CT and/or following endoscopic ultrasound. MRCP provides better imaging of the pancreaticobiliary tree than other imaging modalities, requires no administration of contrast and can identify liver metastases but is dependent upon availability of the resource and relevant expertise.[63]

Positron emission tomography (PET) is a nuclear medicine imaging technique which produces a three dimensional image and is able to distinguish between normal cells and rapidly dividing cancer cells. Sensitivity of PET for pancreatic cancer ranges from 73% to 92% and specificity from 68% to 86%.[63] It can detect pancreatic metastases with about 80% reliability.[67] For this reason it is often used for patients with potentially resectable disease to detect small metastases in the liver or lymph nodes that would suggest resection is an inappropriate course of management.

At the time this patterns-of-care study was completed PET scanning facilities were rarely available in rural or remote areas due to the necessity to regularly transport radioactive material for their use and the extensive requirements and costs of establishing specialised facilities. The number of PET facilities has since increased, with approximately 15 facilities in both QLD and NSW in 2016.[68]

Laparoscopy/laparotomy: A laparoscopy (keyhole surgery) or a laparotomy (open surgery) can be performed by a surgeon to obtain a tissue diagnosis and investigate the resectability of the tumour. This is particularly useful if the imaging is unclear regarding major arterial blood vessel involvement and can prevent the morbidity associated with major surgery. Laparoscopy has been shown to be less reliable than a full laparotomy to predict distant metastases.[69] Although previous reports suggest laparoscopy is able to identify occult metastases in up to 50% of cases, it has been

argued more recently that this proportion has fallen and laparoscopies are no longer required due to the increasing sensitivity of CT scans.[70]

Biomarkers: There are no accurate or tumour-specific diagnostic blood tests available for pancreatic cancer although the carbohydrate antigen 19-9 (CA 19-9) test is widely used. A meta-analysis reported that elevation of CA 19-9 has both a sensitivity and specificity of 80%.[71] CA 19-9 has limited diagnostic use as approximately 10% of the population is unable to synthesise CA 19-9, and levels may also be elevated in patients with other benign pancreatic diseases,[72] and with other gastrointestinal cancers.[73] It should therefore be used alongside other diagnostic techniques in the diagnosis of pancreatic cancer.[60] It is the only biomarker recommended for routine use as an indicator of treatment response and for disease monitoring.[74, 75]

Ongoing investigations and clinical trials are being conducted to determine the clinical significance of screening and diagnostic biomarkers, such as the S100 and MUC proteins,[76, 77] to enable early detection, prognostic biomarkers to predict survival patterns[78] and predictive biomarkers to personalise treatment regimens,[75] Further trials are investigating diagnostic tests to identify circulating tumour cells, although these cells are only likely to be found in patients with metastatic disease, or to detect circulating DNA which has been detected in 43% of patients with localised pancreatic cancer.[79]

1.9.2. Stages of pancreatic cancer

The extent of a pancreatic cancer's growth and spread is routinely classified using the TNM coding system.[80, 81] This was developed by the International Union Against Cancer (UICC)[82] and the American Joint Committee on Cancer (AJCC).[83] The T refers to the size of the primary tumour and whether it has infiltrated to adjacent vessels or organs; the N refers to involvement of regional lymph nodes; and the M refers to whether the cancer has metastasised to distant organs such as the liver or lungs (Table 1-1).[81]

Table 1-1: Current (7th edition) TNM classification for pancreatic cancer

	Primary Tumour (T)
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour limited to the pancreas, ≤ 2 cm in greatest dimension
T2	Tumour limited to the pancreas, > 2 cm in greatest dimension
T3	Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)
	Regional lymph nodes (N)
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
	Distant metastasis (M)
M0	No distant metastasis
M1	Distant metastasis

Classification of the TNM stage for pancreatic cancer is problematic, mainly due to the lack of definition for "extending beyond the pancreas" in the classification of T3. Clinicians debate whether the involvement by tumour of: (1) peri-pancreatic soft tissue or (2) the common bile duct which extends from the pancreas, are classified as "confined to the pancreas" or "extended beyond the pancreas". These issues result in a highly subjective classification of T3.[84] Until recently all T3 tumours were thought to be unresectable, but with the improvement in surgical techniques, resectability of the main blood vessels may be viable;[85, 86] hence the T-stage no longer determines resectability and there is a need to redefine a "T" for such cases.[87]

From the TNM coding the overall stage of the disease can be determined from stage 0 to stage IV with stage IV cancers having the worst prognosis (Table 1-2).

Pancreatic cancer has often progressed to become locally advanced or metastatic at the time of diagnosis.[60] Approximately half of all pancreatic cancer patients are diagnosed with metastatic disease, 10-20% are found to have localised disease confined to the pancreas and 20-30% with locally advanced disease.[12, 33, 58] Large proportions of patients (20 - 50%) have unstaged disease in most population-based studies.[12, 33] In NSW, as recorded by the NSW Cancer Registry, in 2006 17% were diagnosed with localised, 13% with regional disease, 44% had metastatic disease, and 26% unknown stage.[88]

For patients diagnosed with disease confined to the pancreas, median survival is approximately 15-20 months, compared with 10 months for patients with locally advanced disease and 3-6 months for patients with metastatic disease.[21, 89-91]

Table 1-2: Stage of disease according to TNM and clinical classification and United States estimated five-year survival

Stage[a]	TNM[a]	Clinical disease status	Resectability classification	5-year survival[92]
0	Tis, N0, M0	Carcinoma in situ	Resectable	n/a
IA	T1, N0, M0	Localised	Resectable	14%
IB	T2 ,N0, M0	Localised	Resectable	12%
IIA	T3, N0, M0	Locally advanced	Potentially resectable	7%
IIB	T1 - T3, N1, M0	Locally advanced	Potentially resectable	5%
III	T4, Any N, M0	Locally advanced	Potentially resectable	3%
IV	Any T, Any N, M1	Distant metastases	Non-resectable	1%

[a] Stage and TNM classification of disease according to UICC, 7th edition

1.9.3. Treatment

Accurate staging provides the foundation for optimal treatment.[93-95] For patients with stage I and stage IIa disease complete resection of the tumour is advised followed by adjuvant chemotherapy or adjuvant chemoradiation therapy,[6, 96] while for patients with locally advanced or potentially resectable stage IIb or III disease, neoadjuvant treatment is often recommended. Neo-adjuvant treatment enables the latency of the tumour to be observed, preventing needless costs and resultant morbidity of surgery if progression of the tumour occurs, or facilitates surgical resection and improves surgical margins if the tumour responds to treatment.[6, 97-104] The survival benefit of neo-adjuvant treatment is unproven so its use should be restricted to clinical trials,[6] particularly in the absence of agreed criteria to select patients who may become operable. Adjuvant treatment usually consists of chemotherapy alone, although radiation therapy is occasionally prescribed for patients at high-risk of local recurrence (for example if surgical margins were involved) following resection.

Chemotherapy is recommended for patients with Stage IV disease if they have adequate performance status. If patients are unable to receive systemic therapy, have poor performance status or if they have recurrent or metastatic disease, supportive care which includes palliative care and symptom management, should be provided.[6, 21, 105] Palliative radiation therapy is used for patients who have symptomatic local disease or distant metastases.

1.9.4. Surgery

Surgical removal of the pancreatic neoplasm remains the only reliable curative treatment modality but is only possible in about 15-20% of cases.[10, 106] Population-based studies have shown that surgical resection of the primary tumour is under-utilised.[12, 106, 107] Almost a third of all planned pancreatectomies commence but are then abandoned due to the cancer being more extensive than suggested by imaging.[100] Of those patients receiving a complete resection, 70% survive more than one year.[98, 100, 101] Five-year survival among patients who have surgery is approximately 20-25% compared to less than 5% for patients with no resection of their primary tumour.[32, 33, 108]

Depending on the location of the tumour in the pancreas various surgical procedures are performed. For tumours arising in the head or body of the pancreas, a Whipple's procedure (pancreaticoduodenectomy) is usually performed, or occasionally a total pancreatectomy. Tumours in the tail of the pancreas require a distal pancreatectomy, often including removal of the spleen.[109] Distal pancreatectomy is now often performed laparoscopically which results in a decrease in length of hospital stay as well as a decrease in surgical complications. [110] Surgical post-operative complications, including pancreatic fistula, anastomotic leak, blood loss, pancreatic enzyme insufficiency and wound infection, occur in approximately 35-65% of patients following pancreaticoduodenectomy.[111-113]

Systematic reviews and international studies suggest that patients who undergo surgery in a high-case-volume or tertiary academic hospital with an experienced surgeon are more likely to receive optimal care and have better outcomes including longer overall survival (meta-analysis of 5-year survival for high-case volume compared with low-case volume hazard ratio (HR) 0.79; 95% confidence interval (CI): 0.70 - 0.89),[114] lower readmission and mortality rates (meta-analysis of hospital mortality for high compared with low volume (odds ratio (OR) 0.32; 95% CI 0.16 – 0.64),[114] and lower surgical complication rates following surgery.[13, 85, 106, 114-135]

Guidelines are inconsistent about what constitutes a high-case-volume hospital, with the NCCN recommending a minimum of 15 resections per year,[6] the National Cancer Institute Guidelines recommending five[136] and the British Society of Gastroenterology not specifying a particular number.[137] A systematic review of general surgeon case volume suggested that surgeons should perform at least four pancreatic cancer resections each year to maintain expertise and associated better outcomes.[119, 138, 139]

The volume of pancreatic surgery undertaken at the hospital has also been shown to be associated with outcomes for patients in Australia.[140, 141] There is evidence that surgical inexperience, not

solely for the surgeon but for the entire surgical team, for complex surgeries including pancreatic surgery, is detrimental to patient survival outcomes.[142]

1.9.5. Chemotherapy

Chemotherapy can be prescribed as a cytotoxic agent or radio-sensitiser in the adjuvant setting or to relieve symptoms and improve quality of life (QOL) in the advanced disease setting.[8, 143-145] The administration of chemotherapy has increased over time and improves survival and QOL.[3, 12, 91, 124, 146]

Clinical practice guidelines recommend adjuvant chemotherapy to reduce the risk of recurrence following resection of the primary pancreatic tumour.[6, 147] Gemcitabine has been standard chemotherapy administered as adjuvant therapy since the publication of the CONKO-O01 trial which showed an increase in median disease-free survival of 13.4 months for patients receiving gemcitabine compared to 6.9 months for those in the observation alone arm.[143] A recent trial (JASPAC-01) of adjuvant S-1, (an oral 5-fluorouracil drug) versus gemcitabine conducted in Japan was discontinued early on the recommendation of the independent data monitoring committee due to significant results in favour of the S-1 treatment. Follow-up data from the study has shown a statistically significant improvement in survival for patients who received the S-1 compared to those receiving gemcitabine (HR 0.57; 95% CI: 0.44 – 0.72) associated with 24% five-year overall survival for the gemcitabine group compared to 44% for the S-1 group. S-1 is now recommended as the standard of care for resected pancreatic cancer in Japanese patients.[148]

For patients with advanced disease there are limited curative treatment options and symptom control has been the primary aim of management. In 1997 a landmark randomised controlled trial showed that gemcitabine resulted in a modest survival benefit over 5-fluorouracil but it delivered substantial improvements in pain and performance status.[149] Gemcitabine subsequently became the standard of care for first line treatment in patients with advanced disease. There are attempts to find new drug combinations to further improve survival and QOL for patients with advanced pancreatic cancer. A randomised controlled trial in patients with metastatic disease comparing FOLFIRINOX (a combination of fluorouracil, folinic acid, irinotecan and oxaliplatin) to gemcitabine chemotherapy showed an improvement in survival with median survival of 11.1 months compared to 6.8 months.[150] Nab-paclitaxel (Abraxane), paclitaxel bound to the protein albumin, has recently been shown to increase the survival of patients with metastatic pancreatic cancer with 35% surviving 12 months when used in conjunction with gemcitabine, compared to 22% receiving treatment with gemcitabine alone.[151] These more recent chemotherapy regimens with greater

impacts on survival and QOL are now recommended for treatment of advanced pancreatic cancer in patients with good performance status.[151-153]

Side effects of chemotherapy for pancreatic cancer can include nausea and vomiting, bowel changes, mouth ulcers, anorexia, bruising and nerve changes, depending upon which drugs are received.[92] Supportive care only is a feasible option for patients who decide that the treatment:benefit ratio is unacceptable, although it is important that patients reach this decision following discussion with a specialist oncologist.

1.9.6. Radiation Therapy

Radiation oncology is a rapidly advancing field with new modalities and technology being introduced world-wide, such as intensity modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) which are able to deliver high-precision radiotherapy, allowing for higher doses to the pancreatic tumour while minimising the dose to surrounding critical structures. Clinical benefits include reduced side-effects of treatment but the use of VMAT and IMRT in place of standard three-dimensional radiotherapy has not been tested in pancreatic cancer randomised clinical trials.[154, 155]

Radiation Therapy is often prescribed in the adjuvant setting following incomplete resection of the tumour or where there are involved margins following surgery although there is little evidence to suggest the use of adjuvant radiation is beneficial in terms of patient survival.[156-158]

Radiation Therapy also has a recognised role in the treatment of patients with locally advanced disease but who are unsuitable for surgery either as neo-adjuvant treatment with the aim of shrinking the tumour to increase the potential for surgery or as a definitive treatment for patients unsuitable for surgery.[159] Neoadjuvant chemoradiation therapy provides appropriate treatment while allowing identification of patients who develop early metastatic disease who can be spared the morbidity resulting from surgery. A study from the United States using decision tree modelling suggests that neoadjuvant chemoradiation therapy is associated with improved survival and QOL (18.8 quality-adjusted life-months) with lower cost than a surgery first approach (8.7 quality-adjusted life-months) for patients with pancreatic cancer.[97]

For patients with advanced disease or metastases, a meta-analysis has shown that 60% of patients have pain control in response to palliative radiotherapy for pain management.[160]

1.9.7. Supportive Care

Supportive care is primarily targeted at symptom control and improving QOL. Palliative care is an integral part of this support with clinical evidence suggesting that most cancer patients are only referred to palliative care at the end stage of their life; adequate attention to QOL and patient care preferences often occur only days to weeks from the patient's death.[161] This may be important, as a trial of patients with lung cancer showed that early palliative care intervention significantly improved QOL, fewer patients had depressive symptoms (16% early intervention versus 38%) and survival improved (median early intervention 12 months versus 9 months) despite the use of less aggressive care.[162] These results have been confirmed for patients with advanced pancreatic cancer where more intense palliative care has also been shown to diminish the use of chemotherapy within 14 days of death. Hospitalisations, emergency unit or intensive care admissions within 30 days of death were also reduced.[163] Survival benefits of early referral (63% one-year survival for early palliative care intervention versus 48% in the delayed group) to palliative care have also been reported, although the reasons for this are, as yet, unexplained.[164]

Pain is the most frequent symptom for patients with pancreatic cancer but despite the availability of opioids and coeliac plexus blocking, a systematic review suggested that 43% of patients with cancer are undertreated for pain control.[165] Recent data have suggested that Australian patients with pancreatic cancer have high supportive care needs with higher levels of pain, (OR 6.1; 95% CI 2.4 – 15.3), anxiety (OR 3.3; 95% CI 1.5 – 9.3) and depression (OR 3.2; 95% CI 1.7 – 6.0) associated with higher unmet supportive care needs.[166, 167]

1.9.8. Multidisciplinary care

Multidisciplinary care by a team of clinical specialists provides comprehensive and coordinated evaluation and treatment and is suggested as the most effective way to improve the quality of care and manage patients with pancreatic cancer,[21, 130, 168] leading to changes in clinical diagnoses, and improved treatment recommendations in approximately 25% of patients.[169-171] Early review of patients by an expert multidisciplinary team (MDT) in a high-volume hospital following diagnosis of pancreatic cancer enables accurate staging, comprehensive and coordinated evaluation and optimal management.[21, 94, 126, 172, 173] Patients were more likely to receive treatment, multimodality therapy and participate in a clinical trial if evaluated by a MDT at a tertiary centre.[122, 130] In the United States, implementation of a hepatobiliary (HPB) surgeon-led MDT meeting in regional areas suggested that the general quality of care provided improved, increasing regional referrals from 17% to 44% and tripling the number of HPB surgical procedures.[174] A systematic review of

international literature and a Canadian pilot project found that multidisciplinary care should be managed by MDTs at large tertiary hospitals but smaller or regional centres can benefit by improving access to expert staging, treatment management plans and palliative care by having MDT meetings via telehealth with high-volume tertiary centres.[175, 176]

The European Partnership Action Against Cancer consensus group formulated and approved a policy statement on multidisciplinary cancer care.[90] This document identifies MDTs as essential instruments of effective cancer care and describes the key elements of the MDT including the MDT care objectives, organisation, clinical information, patient-centred approach, and policy support.[94] While there is some debate about what constitutes a MDT,[177-179] it has been suggested that an MDT for the management of patients with pancreatic cancer should include at least one each of; hepatobiliary (HPB) surgeon, medical oncologist, radiation oncologist, interventional radiologist, allied health practitioners including dieticians, social workers, care-coordinator / nurse / General Practitioner, and pathologist.[94, 180-182] Palliative care specialists are often included as their role in supportive care and their ability to provide a continuum of care is realised.[94]

Communication is a major contributor to the care of the patient, with patients stating that they require clear communication and for their clinicians to be on the "same page", not being given contrary advice by different care givers.[183] Bringing clinicians together in multidisciplinary meetings facilitates and encourages inter-clinician communication as well as patient-clinician communication and ensures all care givers have the same information, improving the consistency of care plus MDT and patient collaboration.[184, 185]

Currently in Australia MDTs are recognised as providing optimal quality care by Cancer Australia,[180] but are unregulated and are not a necessary requirement as a clinical standard by National Safety and Quality Health Service Standards for health service organisation accreditation.[186] A survey completed by 267 MDT attendees across Australia revealed that 86% agreed that MDTs improved the outcomes and quality of care received by patients.[172]

1.9.9. Clinical practice guidelines

While there are no comprehensive clinical practice guidelines for the management and treatment of patients with pancreatic cancer in Australia, such guidelines exist from Europe and the United States. However, a recent consensus review of existing guidelines indicated that there is considerable disagreement regarding guideline recommendations primarily due to the lack of high-level evidence available.[187]

Current expert opinion and recommendations from the World Congress on Gastrointestinal Cancer (Barcelona 2006)[4] provide recommendations including the use of appropriate diagnostic tests, adequate staging, multidisciplinary team decisions about resectability, adjuvant treatment and for patients with unresectable disease, chemotherapy with or without radiation. The European Society for Medical Oncology and European Society of Digestive Oncology (ESMO-ESDO) guidelines were updated in 2010 and describe guidelines for care from diagnosis until supportive care.[5, 105, 188]

There are also comprehensive guidelines available through the National Comprehensive Cancer Network (NCCN) in the United States[6] for the management of pancreatic cancer from diagnosis, staging, treatment to follow up. Less detailed guidelines are available from the United States government's National Cancer Institute.[189] Some details of guidelines are provided in the table below (Table and Table 1-4).

In Australia, the State of Victoria's Department of Health and Human Services has published a practical optimal care pathway for people with pancreatic cancer which summarises steps from prevention and detection, through treatment to communication and end-of-life care.[95] This pathway was developed by the National Cancer Expert Reference Group established by the Council of Australian Governments in 2010. The NSW Government with the Cancer Institute NSW have several clinical evidence-based, quality controlled cancer treatment protocols on-line (eviQ). Chemotherapy treatment regimens for pancreatic cancer and links to the Cancer Institute NSW are available through the eviQ website and are accessible to anyone following registration.[190]

The Australian Gastro-Intestinal Trials Group (AGITG) has recently published a set of consensus guidelines defining surgical resectability, calling for MDT assessment prior to surgery, structured pathology reports and discusses the use of neo-adjuvant therapy.[159]

Table 1-3: American and European Guidelines for the diagnosis, staging and management of resectable or locally advanced pancreatic cancer

Guidelines	Diagnostic and Staging Investigations		Surgery	Chemotherapy	Radiation	Other
Resectable disease						
ESMO-ESDO [105]	Pancreas protocol CT Selected cases MRI and laparoscopy. CA 19.9- limited use. Small tumours EUS + FNA. Pathological proof is mandatory except for radical surgical cases.	Staging using AJCC-UICC classification. MRCP. EUS. Not PET. ERCP only therapeutic use.	Radical for early stage. Margins clear to 1mm. LNR should be reported.	Adjuvant- 6 cycles 5FU or gemcitabine. Neoadjuvant in trial setting only.	Should only give adjuvant RT in trial setting.	
NCCN[6]	Pancreas-protocol CT. MRI. ERCP- if clinically indicated or MRI/CP.	EUS. Chest CT. Biopsy. Staging laparoscopy. PET only to detect mets in high-risk patients.	Complete guidelines re surgical procedure and pathology reporting.	Adjuvant, Gemcitabine or 5FU before or after CRT or Gemcitabine. 5FU. Capecitabine. Single agents.	CRT followed by 5FU or Gemcitabine Chemo then CRT With surgery 6-8 weeks after CRT.	
Locally advanced disease						
ESMO-ESDO[105]	Pancreas protocol CT. MRI EUS	MRCP Pathological proof is mandatory.		Neoadjuvant: either chemo then CRT or direct CRT. Gemcitabine 3 months.	Should only give neo/adjuvant RT in trial setting.	
NCCN[6]	Pancreas protocol CT. MRI	EUS. Chest CT. ERCP- if clinically indicated or MRI/CP. Biopsy.		Neoadjuvant CRT or chemo then CRT Gemcitabine, capecitabine, 5FU	Neoadjuvant CRT or chemo then CRT 36 - 54 Gy	Biliary bypass or stent Coeliac plexus block

Table 1-4: American and European Guidelines for the diagnosis, staging and management of metastatic pancreatic cancer

Guidelines	Clinical work-up	Chemotherapy	Radiation	Other
Metastatic/unresectable disease				
ESMO[5]	CT, MRI, biopsy PS, Comorbidities, Geriatric assessment.	Gemcitabine, 5FU, Oxaliplatin, abraxane in combination preferably on trial.	Pain control only.	Endoscopic stenting- metal if life expectancy > 3 months. Pain- opioids, coeliac axis block.
NCCN[6]	Pancreas-protocol CT. MRI, PS, Biopsy	Depending on performance status. Trial preferred Gemcitabine, Capecitabine, Oxalyplatin, FOLFIRINOX, Abraxane in any combination.	Trial preferred. 30-36 Gy for palliation. Palliative RT for patients suitable for definitive treatment but have poor PS or comorbidities	Pancreatic enzyme replacement. Biliary bypass or stent. Coeliac plexus block. Poor performance status - best supportive care

ESMO: European Society for Medical Oncology; ESDO: European Society for Digestive Oncology; NCCN: National Comprehensive Cancer Network; CT: computerised tomography; MRI : magnetic resonance imaging, EUS: endoscopic ultrasound; ERCP endoscopic retrograde cholangio-pancreatography; FNA: fine needle aspiration; LNR: lymph node ratio; CRT: chemo-radiation therapy; PET: positron electron tomography; PS: Performance status; CRT : chemoradiation therapy; 5FU: 5-Flourouracil RT: radiotherapy; Gy: Gray (radiation dose)

1.10. VARIABILITY IN CARE OF PATIENTS WITH PANCREATIC CANCER

Research on patterns of care describes clinical practice and explores variability in care. It can be used to inform educational programs designed to improve the quality of care at the patient, clinician or policy level.[191] To investigate the current receipt of therapies and patterns of care internationally and in Australia for patients with pancreatic cancer I undertook a search of PubMed to find relevant articles and identified 29 patterns-of-care studies, excluding small single centre studies with samples of less than 200; these are shown in Appendix C, Table 9-1.

Most of these studies were completed in the United States (n=18), with seven from Europe and Scandinavia, one from Canada and three from Australia. Sample sizes for the studies ranged from 219 patients in Norway to over 300,000 in the United States. The earliest data collected was from 1983 in the United States and the most recent from 2012 in Norway. Some studies focussed on sub-groups of patients, with four studies focussed on patients with metastatic disease, three describing care of patients following resection, three on patients with non-metastatic disease and one on patients with locally advanced disease. The studies varied in quality with most unable to adjust for known confounders such as receipt of chemotherapy and performance status, while some studies were not specific for pancreatic adenocarcinoma.[62, 192-195]

Only four studies did not identify patients using cancer registry notifications.[196-199] Most of the studies, especially those from the United States used electronic administrative datasets containing information on the patients' diagnosis, treatment and management to provide results, including the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database and the National Cancer Data Base (NCDB). The NCDB collects data on approximately 70% of all new invasive cancer diagnoses each year[200] and the SEER database collects data from geographical areas covering approximately 28% of the United States population.[201] Procedures and treatments are generally under-recorded in administrative databases.[202] For example, the SEER database does not release data on chemotherapy receipt due to a recognised incompleteness of the data.[203] Another deficiency of administrative data is the lack of reporting of some patient factors, including performance status which is a known determinant of active treatment such as surgery and chemotherapy due to the increased risks of morbidity.[151, 204, 205] Performance status is also a major prognostic factor for survival for all stages of pancreatic cancer.[206, 207]

Cohort characteristics and overall receipt of treatment reported in the included studies are summarised in Table 1-5. Approximately 50% of all patients were diagnosed with metastatic (Stage

IV) disease and this is relatively consistent across all studies. Fewer than 15% of all patients proceeded to surgical resection, with an average of 7% (range 3% - 11%) in Europe, and 15% in the United States (range 9% – 22%). The studies suggest that the use of adjuvant chemotherapy has increased in more recent years; studies published from 2013 onwards report that 75% or more of patients received adjuvant chemotherapy compared with approximately 40% of patients in studies including patients diagnosed and treated prior to 2005. Reports suggest between 20% and 42% of patients received palliative chemotherapy. All treatments were administered to a greater proportion of patients in the United States than in Europe, in particular radiation therapy (United States 25% compared to 8% in Europe).

1.10.1. Care of pancreatic cancer patients in Australia

Australian health care is unique in terms of geographical complexity and the mix of public and private facilities. The Australian government supports care in both public and private facilities. Care is provided free in public hospitals while care in private facilities is co-funded by contributions from private health insurance companies and patients. In Australia in 2007-2008 approximately 95% of outpatients occasions of service occurred in public hospitals and 60% of all surgery was completed in private hospitals.[208] Hospitals are accredited by the government to provide medical services. Large metropolitan hospitals usually have a full range of services compared to smaller regional hospitals which often primarily provide aged or supportive care. Despite some degree of regulation, a lack of centralisation of cancer care exists. Between 2005 and 2008 in NSW pancreatic cancer surgery took place at 37 hospitals with almost half of them (n = 15, 41%) undertaking fewer than two procedures each year.[209] For patients diagnosed with pancreatic cancer in QLD, only three formal MDT meetings are held weekly throughout the state, all in metropolitan tertiary hospitals.

Few Australian population-based studies describing the care of patients with pancreatic cancer were identified. A QLD government report described pancreatic surgery, showing that pancreaticoduodenectomy was performed on 12% of patients diagnosed during 2009-2011.[192] A NSW government report described the hospital volume of facilities providing pancreatic surgery, observing that 41% of hospitals performing pancreatic resections between 2005 and 2008, undertook two or less pancreatic resections annually.[209] A population-based Victorian research study reported that during 2002 and 2003 11% of patients had a complete resection, 52% of these had adjuvant chemotherapy and that 16% of the cohort had radiation therapy and 32% palliative

chemotherapy. This study found that only 6.8% of patients diagnosed with pancreatic cancer were managed by a MDT.[18]

Table 1-5: Pancreatic cancer stage and receipt of treatment reported in identified patterns-of-care studies

First author, year	Data	Country N	Disease stage (%)				% surgery	% chemotherapy	% adjuvant chemotherapy	% radiotherapy	% palliative chemotherapy	% MDT review
			Localised or stage I / II	Regional or Stage III	Distant or stage IV	Unknown	All patients		Surgical resection			
United States												
Wolfson, 2015[123]	All 1998 - 2008	United States, Los Angeles 2,317	22	15	56							
Abraham, 2013[10]	All 1994 - 2008	United States, California 20,312			46		15		Any adjuvant treatment 83	12	Unresectable 42	
Oberstein, 2013[210]	Distant disease > 65 years 1998 - 2005	United States, SEER and Medicare 3,094									42	
DaCosta, 2013[196]	All 2001 - 2010	United States Managed care 5,262			50		16	47	41			
Singal, 2012[211]	Non-metastatic 1998 - 2008	United States, SEER data 16,282	20-25	75-80	-					19-22		
Gong, 2011[33]	All 1995 - 1999	United States, San Francisco 1,954	7	27	47	7	11	Chemo or radiotherapy 21	-	Chemo or radiotherapy 21	-	
Davila, 2009[212]	Resected and > 65 years 1992 - 2002	United States, SEER-Medicare data 1,383	70	3	-	25	-	-	40	Adjuvant 39	-	
Shavers, 2009[213]	All 1998	United States, SEER data 697			62		14	42		20		[10]
Bilimoria, 2007[13]	All 1985 - 2003	United States 301,033	32	13	55		13	8	1995 -2003 Stage I and II 40	1995 -2003 Stage I and II 36		
Cress, 2006[89]	All 1994 - 2000	United States 10,612	7	34	51	9	16	-	Any adjuvant treatment 58	Adjuvant 39	-	
Eloubeidi, 2006[195]	All 1996 - 2000	United States, Alabama 2,230	12	30	35	23	22	31		14		

First author, year	Data	Country N	Disease stage (%)				% surgery	% chemotherapy	% adjuvant chemotherapy	% radiotherapy	% palliative chemotherapy	% MDT review
			Localised or stage I / II	Regional or Stage III	Distant or stage IV	Unknown	All patients		Surgical resection			
Krzyzanowska, 2003[214]	Unresected, LAD 1991 - 1996	United States, SEER and Medicare 1,696			-		-	**31**	-	**37**	-	
Senner, 1999[215]	All 1985 - 1995	United States, NCDB 100,313	20	12	33	34	9	30	33	23	30	
Janes, 1996[197]	All 1983 - 1985 + 1990	United States 16,942	26	16	57	25	10	37		26	Stage IV 26	
Wade, 1996[199]	All 1989 - 1994	United States, 698					16					
Canada												
Kagedan, 2016[216]	All 2005 -2010	Canada, Ontario 6,296					13		Any adjuvant treatment 75			
Europe												
Jooste, 2016[217]	All 2009 - 2011	France 554			54							
HajMohammad, 2016[131]	Metastatic 2007 - 2011	Netherlands 5,385			54 of all PC						24	
Bernards, 2015	Metastatic 1993 - 2010	Netherlands 1,494			2009-2010 59						27	
Sharp, 2009[12]	All 1994 - 2003	Ireland 3,173	5	13	46	37	7	12	39	7	20	
David, 2009[62]	All 2001 - 2005	France, 2,986	9	6	86		11	42	40	9	42	
Bramhall, 1995[193]	All 1957 - 1986	UK, West Midlands 13,560					1977 -1986 3					
Australia												
Queensland Health, 2015[192]	All 2009 - 2011	Australia, QLD 664					13					
Jefford, 2010,[18] Speer, 2012[107]	All 2002 - 2003	Australia, VIC 765	20	4	76		11	36	52	16	32	7

Missing data indicates that the % of patients is unable to be determined from publication results.

PC: Pancreatic cancer; SEER: Surveillance; Epidemiology and End Results program; NCDB: National Cancer Database; LAD: Locally advanced disease; UK:United Kingdom.

1.11. DETERMINANTS OF ACCESS TO CARE

Access to treatment for patients diagnosed with pancreatic cancer is not always equitable. Factors associated with being less likely to receive surgery are shown in Table 1-6 and with receipt of chemotherapy or radiotherapy in either the adjuvant or palliative setting are shown in Table 1-7.

These studies suggest that elderly patients with pancreatic cancer are less likely to receive surgery (approximate OR: 0.20 for each increasing decade) or any chemotherapy (approximate OR of 0.40 for each increasing decade) than younger patients, although there is evidence of benefit of treatment in selected older patients.[218-220] The presence of a higher number of co-morbidities also reduces the likelihood of receiving surgery (comparing increasing number of comorbidities with none) (OR 0.26; 95% CI: 0.08 – 0.83) or chemotherapy (0.79; 95% CI 0.66 - 0.93).[210, 213] Pancreatic cancer treatment poses significant morbidity, so taking patient factors such as age, co-morbidities and patient preferences into account may be appropriate. The lower use of surgery or chemotherapy in patients living in lower socio-economic areas or more rural areas indicates inequitable access to treatment. A recent Canadian study estimated the odds of receiving surgery decreased with decreasing socio-economic status (SES) (comparing the lowest SES quintile with the highest OR 0.49; 95% CI 0.37 – 0.64) although it found no statistically significant difference in the receipt of chemotherapy.[216] Other international studies have estimated significant differences with approximately twice the odds of receiving surgery or chemotherapy for patients in patients with high SES as those with low SES.[11, 210, 221]

Patients who presented to or received treatment in larger or specialised cancer centres were more likely to receive surgery or chemotherapy (OR range: 1.20 to 2.20).[13, 131] Due to the increasing evidence that better outcomes are achieved for patients with pancreatic cancer if they receive their staging and treatment at specialised high-volume centres, there have been efforts to centralise care in the last five years.[121, 129]

Although there are indications that centralisation of care has been occurring in Australia, recent government reports indicate some surgery is still performed in low-case-volume hospitals.[192, 209] A QLD report indicates that between 2002 and 2011, 23 hospitals performed pancreaticoduodenectomies but this number had dropped to 13 by 2011.[192] Of the 37 hospitals in NSW that performed pancreatic resection for cancer in the period 2005-2008, only six (16%) performed more than six procedures on average each year. There were also 15 (41%) hospitals undertaking two or fewer procedures annually on average during this period.[209] NSW surgeons performing between four and six pancreaticoduodenectomies each year within a hospital with a

high-volume of upper-gastrointestinal surgery have comparable outcomes to those achieved by high-case-volume international centres.[141] We found no Australian studies describing the determinants of pancreatic surgery or receipt of chemotherapy for patients diagnosed with pancreatic cancer.

Table 1-6: Review of factors associated with receiving surgery for pancreatic cancer

First author	Data	Country N	Facility Case Volume[a]	Race	Age	Sex / comorbidities	Rural	SES [b]
				Black vs White		Men vs. Women	Urban vs. Rural	Lowest vs. highest quintile
Kagedan, 2016[216]	All 2005 -2010	Canada, Ontario 6,296					Rural vs. Urban OR: 0.68, 0.51–0.91	OR: 0.49 (0.37–0.64)
Queensland Health, 2015[192]	All 2009 - 2011	Australia, QLD 664		17% (Indigenous) vs. 13% (Non)	20%(<65 yrs) vs. 4% (75+ yrs)	15% vs. 10%	13% vs. 11%	15% (affluent) vs. 12%(disadvantaged)
Abraham, 2013[10]	All 1994-2008	United States, California 20,312		OR: 0.66 (0.54-0.80)	75-79 yrs vs. <65 OR: 0.26 (0.22-0.31)	OR: 0.95 (0.85-1.1)		No Medicaid vs. Medicaid OR: 1.7 (1.4-2.2)
Seyedin, 2012[11]	Non-metastatic 1998-2002	United States, SEER data 5,908	-	OR: 0.65 (0.52-0.82)		Women vs. Men OR: 0.82 (0.72-1.01)		OR: 0.52 (0.35-0.78)
Singal, 2012[211]	Non-metastatic disease 1998-2008	United States 16,282		19% vs. 18%				
Sharp, 2009[12]	All 1994-2003	Ireland 3,173			75+ yrs vs. <65 OR: 0.18 (0.11–0.28)			
Shavers, 2009[213]	1998	United States, SEER data 697		n/s	Increasing year OR: 0.98 (0.95–1.00)	Charlson score 2+ vs. score 0 OR: 0.26 (0.08 – 0.83)		Uninsured vs. Insured OR: 0.09 (0.01–0.62)
Bilimoria, 2007[13]	Stage I&II: 1985-2003	United States 301,033	Highest vs. Lowest quartile OR: 1.45 (1.35–1.55)				OR: 1.26 (1.1 –1.36)	
Eloubeidi, 2006[195]	All patients 1996-2000	United States, Alabama 2,230		14% vs. 17%, p=0.09				
Cress, 2006[89]	All 1994-2000	United States 10,612		13% vs. 17%, p=0.03				48% (High) vs. 44% (Low), p= 0.02
Janes, 1996[197]	All 1983-1985, 1990	United States 16,942	14%(< 10 cases) vs. 17% (>20 cases)	12% vs.15%	22% (<50 yrs) vs. 8% (80+ yrs)			17% (Highest income) vs. 13% (Lowest)

[a] Facility case volume = pancreatic cancer surgery or pancreatic cancer caseload volume, higher academic or tertiary facility if no facility volume recorded.

[b] based on socio-economic status (SES) or insurance status

Table 1-7: Review of factors associated with receiving chemotherapy or radiotherapy treatment for pancreatic cancer.

First author	Data	Country N	Facility Case Volume[a]	Race	Age	Sex/ Comorbidities	Rural	SES[b]
			Highest vs. Lowest quartile	Black vs White	years (yrs)	Men vs. Women	Urban vs. Rural	Highest vs. Lowest quintile
Any adjuvant treatment								
Kagedan, 2016[216]	All 2005 -2010	Canada, Ontario 6,296		OR: 0.98 (0.78–1.22)				Increasing deprivation OR: 0.95 (0.70–1.28)
Abraham, 2013[10]	All 1994-2008	USA, California 20,312		OR: 0.75 (0.58-0.98)	75-79 vs. <65 yrs OR: 0.29 (0.23-0.37)	OR: 1.1 (1.0-1.2)		Uninsured vs. Insured OR: 0.54 (0.30- 0.98)
Davila, 2009[212]	> 65, post-op 1992-2002	USA, SEER data 1,383	OR: 1.85 (1.20–2.86)	OR: 0.61 (0.38–0.99)	75 + vs. 65-75 yrs OR: 0.43 (0.34-0.54)	OR: 1.17 (0.93–1.47)	Rural vs. Urban OR: 0.92 (0.23–3.76)	OR: 1.64 (1.10–2.47)
Bilimoria, 2007[13]	Stage I&II: 1985-2003	USA 301,033	OR:1.20 (1.10–1.32)				OR:0.89 (0.79–1.01)	
Chemotherapy								
HajMohammad 2016[131]	Metastatic 2007-2011	Netherlands 5,385	OR: 2.20 (1.85–2.61)					
Bernards, 2015[221]	Metastatic 1993-2010	Netherlands 1,494			80+ vs. 60-69 yrs OR: 0.04 (0.01–0.18)	Women vs. Men OR: 0.91 (0.67–1.24)		OR: 2.05 (1.34–3.13)
Vijayvergia, 2015[198]	Metastatic 2000-2010	USA, 579			75% (<65 yrs) vs. 65% (65+), p <0.001			
Oberstein, 2013[210]	Metastatic 1998 -2005	USA, SEER data 3,094		OR: 0.73 (0.57–0.93)	85+ vs. 65-69 yrs OR: 0.20 (0.14–0.27)	Women vs. men[c] OR: 0.80 (0.70-0.93)	OR: 1.07 (0.84–1.38)	OR: 2.14 (1.66 -2.76)
Sharp, 2009[12]	All 1994-2003	Ireland 3,173			75+ vs. <65 yrs OR: 0.04 (0.02-0.07)	OR: 1.11 (0.85–1.46)		
Shavers, 2009[213]	1998	USA, SEER data 697		OR 0.61 (0.37–0.95)	Increasing year OR: 0.94 (0.92–0.96)			Uninsured vs. Insured OR: 0.36 (0.11–1.21)
Eloubeidi, 2006[195]	All patients	USA, Alabama 2,230		27% vs. 32%, p = 0.02				
Radiation therapy								
Shavers, 2009[213]	1998	USA, SEER data 697		OR 0.74 (0.42–1.30)	Increasing year OR: 0.97 (0.95–0.99)			Uninsured vs. Insured OR: 1.82 (0.56–5.96)
Combined modality treatment or cancer directed therapy								
Krzyzanowska, 2003[214]	Unresected, LAD[d] 1991-1996	USA, SEER data 1,696	Teaching OR: 1.26 (1.01–1.57)		Increasing decade OR: 0.43 (0.37–0.51)	Increasing Comorbidities OR: 0.85 (0.75–0.96)	Midwest United States (West United States ref) OR: 1.60 (1.26–2.03)	Increasing quintile OR:1.15 (1.06–1.24)
Janes, 1996[197]	All 1983-1985, 1990	USA 16,942	45%(< 10 cases) vs. 55% (>20 cases)	47% vs. 54%	70% (< 50 yrs) vs. 25% (80+ yrs)			58% (High) vs. 48% (Low)

[a] Facility case volume= pancreatic cancer surgery or pancreatic cancer caseload volume, or academic or tertiary facility status; [b] Based on socio-economic status (SES), material deprivation or insurance status; [c] Comorbidities also reported: 2+ comorbidities (0 ref) OR: 0.79 (0.66 - 0.93) ; [d] LAD locally advanced disease; OR: Odds ratio (95% confidence interval)

1.12. QUALITY OF CARE

Evidence-based care that is in accordance with guidelines is generally accepted as high-quality care.[119] Indicators based on the receipt of guideline-recommended care[222] provide benchmarks to facilitate the measurement of the quality of care delivered.[134]

Quality indicators for pancreatic cancer care have been developed in the United States by reviewing the literature, consensus guidelines and expert interviews. These indicators include quality indicators measured at both the hospital and the patient level.[119] Similar to clinical guidelines from the United States, these indicators are primarily associated with pancreatic surgery and include monitoring the hospitals and surgeons' case volume, recording clinical or histological stage, provision of care in an intensive care unit, access to interventional radiology, radiation and chemotherapy services if performing pancreatic surgery and monitoring stage-specific survival. When these quality indicators were measured, compliance with guidelines at the individual patient level ranged from 50% to 97% and at the hospital level compliance ranged from 7% to 100%.[119]

A United States study of 3,706 patients in 50 hospitals found patients with pancreatic cancer had a reduced likelihood of death from any cause (OR 0.64; 95% CI 0.53 – 0.77), after controlling for patient and hospital factors, if they received care compliant with the NCCN guidelines.[222] Patients with lower SES (comparing the lowest SES quintile with the highest OR 0.61; 95% CI 0.47 - 0.80), who were older in age (comparing patients aged 75-84 years with aged <45 years OR 0.30; 95% CI 0.20 – 0.44) and seen in lower case-volume hospitals were less likely to have care compliant with NCCN guidelines.

While the measures of quality of care for patients are linked to clinical practice guidelines they do not necessarily reflect all aspects of care relevant to optimising the patient experience. Quality indicators are best derived by experts in the field and a Delphi process is one established method to harness these experts' opinions.[223]

1.13. DELPHI PROCESS

The Delphi process was first developed in the 1950s[224] and has been used in a wide-range of fields including the military service, medicine and education to elucidate experts' views regarding their specialty.[225] The value of the Delphi process for developing expert consensus on clinical health-related decisions and for selecting healthcare quality indicators has been demonstrated through its extensive use in Australia and internationally.[226-230]

1.13.1. Delphi process characteristics

A Delphi process is iterative, consisting of approximately three rounds.[231] The first round generally asks experts an open-ended question and subsequent survey questions are based on the responses to this. The experts are asked to rank or score each questionnaire item. The results of this scoring process are compiled. Participants are then asked to re-score the items with knowledge of the mean score elicited in the previous questionnaire round. The process is repeated until consensus (see below) with item scores, between the panel participants is reached.

Advantages of the Delphi process are that it enables group communication that might otherwise have been impossible due to time, geography or other constraints.[232] It also draws together existing knowledge and pinpoints areas of agreement or disagreement.[232] Furthermore, the anonymity of participants provides them with the opportunity to freely express opinions and positions.[233] Disadvantages include a potentially high attrition rate as the process is time-consuming and requires active participant engagement over several weeks or even months.[234] Potential costs of producing surveys and correspondence have been reduced by the use of the eDelphi process which uses online surveys and electronic correspondence rather than the traditional written paper method.[235]

1.13.2. Delphi participants

The Delphi process has been criticised for its lack of definition of an expert and for the impact on the reliability and accuracy of the outcomes by including non-experts on panels.[236] Others have suggested that a heterogeneous group of participants increases the variety of opinions and is beneficial to the outcomes of the Delphi process and that participants with diverse perspectives produce more accurate judgements.[237, 238]

The sample size used in surveys varies from 2 to 1000. The general consensus is that between 20 and 50 is adequate to develop reliable criteria that inform judgment and support effective decision making,[233] but that the larger the participant group the more reliable the collective outcomes will be.[232]

1.13.3. Delphi consensus and results

The Delphi process aims to bring participants to consensus, stopping when further rounds are unlikely to change the results. However, there is no standard method for determining consensus. A study to compare methods of declaring consensus analysed data from a Delphi process using the

Pearson correlation coefficient, F-test and the coefficient of variation. It found that the coefficient of variation was the most reliable method for predicting consensus and that, in general, two rounds of scoring was sufficient to reach consensus, with negligible improvement thereafter.[231] The coefficient of variation is a standardised measure of dispersion and is useful for the comparison of distributions of Delphi scores. It is the ratio of the standard deviation to the mean for each item score and is usually reported as a percentage by multiplying the ratio by 100. In Delphi research, assorted studies have used the coefficient of variation as a measure for consensus as it allows for a direct comparison between rounds and also of the stability of results amongst groups or individuals.[226, 239] A high degree of consensus is generally accepted as represented by a coefficient of variation of ≤ 0.5, 0.5 to ≤ 0.8 indicate less than satisfactory consensus and > 0.8 a low degree of consensus.[226]

1.13.4. Application of the Delphi Process to Pancreatic cancer

Recently, a core set of patient-reported outcomes for patients with pancreatic cancer was compiled using a two-round Delphi process in the Netherlands. The 150 patients and 78 health care practitioners, reached consensus for 17 patient-reported outcomes which included general quality of life, physical ability, negative feelings and satisfaction with services.[240] Bilimoria used an adaptation of the Delphi process to develop clinical quality indicators to evaluate pancreatic cancer care and to identify potential quality improvement opportunities. A two-round Delphi process, with an expert panel of 20 specialist clinicians, rated 43 out of 50 potential indicators as valid. These included measures of clinical processes of care, treatment appropriateness, efficiency, structural factors and outcomes.[119] The Delphi method was also used to develop research priorities for pancreatic cancer in Australia in 2010.[184] While these Delphi processes did harness opinions regarding pancreatic cancer care they did not determine which aspects of care or management were most important, and they did not evaluate the effectiveness of adherence to the indicators with patient outcomes.

With the diversity of Australian geography and health-care a Delphi process is an optimal method for determining aspects of care important in the care and management of patients diagnosed with pancreatic cancer.

1.14. LITERATURE REVIEW SUMMARY

Clinical management of pancreatic cancer is complex and challenging. Patients with pancreatic cancer have poor survival with mortality rates similar to incidence rates, and there has been little

improvement in survival over the past several decades. While there is increasing research into new screening tests, diagnostic investigations and treatments, improving the quality of care and ensuring equitable access to that care could deliver improved outcomes even in the absence of new treatment options. Enabling all patients to be managed by high-performing multidisciplinary teams will also enable full realisation of benefits expected to accrue from the development of new therapies over the coming decades.

This literature review has described current clinical practice guidelines and described appropriate care for patients diagnosed with pancreatic cancer. Randomised trials and a population-based study have found that survival outcomes can be improved by increasing the proportion of patients undergoing resection and chemotherapy.[12, 124, 146] In Australia there are no national clinical guidelines and, with the diverse socio-demographic characteristics in Australia and a unique health-service system, definition of optimal care for patients diagnosed with pancreatic cancer is required. Australian quality indicators are also required to help identify where changes in policy and/or practice could be implemented to improve patient outcomes.

Population-based studies have provided evidence that care of patients with pancreatic cancer is varied, effective treatments are under-utilised and that compliance with recommended clinical guidelines is sporadic. International pancreatic cancer clinical guidelines are inconsistent, but even in countries where there are clear guidelines evidence suggests that the care and management of patients with pancreatic cancer varies according to patient, socio-demographic and health-service factors. Accurate staging and evidenced-based treatment is most likely to be achieved by experienced multidisciplinary teams specialised in caring for patients with pancreatic cancer at a high-volume hospital. How often this occurs in Australia is unknown.

Australian data, on a population-level, are needed to generate information about the management of patients with pancreatic cancer and to identify factors determining variability in that management. Data are also needed to describe evidence-based optimal care and to evaluate the benefits of this care. Knowledge of the patient, socio-demographic or health-service factors associated with access to this care is also required for Australia.

These data will provide a baseline against which the effect of changes in policy and practice can be measured. By improving management of the disease and by providing all patients with equitable access to optimal care, we can almost certainly have an impact on survival and quality of life for patients diagnosed with pancreatic cancer.

Chapter 2: Aims and Hypotheses

2.1. RESEARCH AIMS

The over-arching aim of this research was to gain an in-depth understanding of the management and care of patients diagnosed with pancreatic cancer in Australia, thereby identifying avenues for improvement.

The specific research aims were to:

1. Identify indicators of care that clinicians believe important in the management of patients with pancreatic cancer
2. Describe the proportions of pancreatic cancer patients who receive different treatment modalities.
3. Identify determinants of variability in delivery of cancer-directed therapies.
4. Determine if patient, tumour or health service factors influence survival for patients with non-metastatic disease.
5. Develop a quality-of-care score based on the indicators of care identified by clinicians and (a) investigate factors associated with the quality-of-care score; and (b) examine the association between the quality-of-care score and overall survival.

2.2. HYPOTHESES

The overall hypothesis of this research was that the quality of care and outcomes for patients diagnosed with pancreatic cancer in NSW and QLD varies according to patient, tumour and health-service factors. Specific alternative hypotheses include:

A. Clinical specialists in pancreatic cancer management throughout Australia can identify and reach consensus regarding factors required to provide optimal care for patients diagnosed in Australia.
B. Management of pancreatic cancer patients in NSW and QLD varies and is influenced by patient, tumour and/or health-system factors.
C. Patient, tumour and/or health-system factors influence the overall quality-of-care score.
D. The quality-of-care score is associated with survival.

Chapter 3: Methods

A variety of processes and analytical methods was employed to investigate the patterns and determinants of care, including the development of clinical quality indicators and a quality-of-care score, for patients diagnosed with pancreatic cancer. The analytical methods used to complete the aims and objectives of my PhD are explained in detail in each of the publications (Chapters 4 to 7 and Appendix H). This chapter describes in more detail the data collection, data management, quality control and derivation of the variables used in the analyses. My contribution to these processes is also explained.

My research is nested within the pancreatic cancer patterns-of-care study with Associate Professor Rachel Neale as the principal investigator. The patterns-of-care study received NHMRC funding in 2010 (NHMRC grant number 613654). I also conducted a sub-study to develop clinical quality indicators and a quality-of-care score to complement the data collected in the patterns-of-care study.

3.1. PATTERNS-OF-CARE STUDY

The patterns-of-care study was a population-based retrospective medical record review of all patients diagnosed with pancreatic cancer in QLD and NSW between July 2009 and December 2010 (NSW) or June 2011 (QLD). Data collection for the patterns-of-care study began in April 2010 and was completed in March 2013.

The data from the patterns-of-care study were used to describe management patterns and survival outcomes and to quantify the quality of care for patients with pancreatic cancer.

3.1.1. Patterns-of-Care Study Participants

Patients were identified by the cancer registries in NSW and QLD. Eligibility criteria for the study included all patients (including death certificate only) who were:

- aged 18 years or older,
- diagnosed between 1st July 2009 and 30th June 2011 and notified to the QLD Cancer Registry or between 1st July 2009 and 31st December 2010 and notified to the NSW Cancer Registry (Cancer Institute NSW)
- diagnosed with pancreatic cancer (ICD-10 code C25).

3.1.2. Cancer Registry Data

Cancer notification is mandatory in Australia with data sourced from hospital records, pathology reports, death certificates and general practice. Data collected are of sufficiently high quality to comply with the International Association of Cancer Registries external conventions and be included in the Cancer Incidence in Five Continents reports.[241]

Data quality is maintained by validating data entry, auditing coding accuracy, monitoring notifications, reconciling information from multiple sources, examining multiple registrations, collaboration between other registries and medical experts and verifying cases using the electoral rolls.

Discrepancies found between patients identified for the patterns-of-care study by the cancer registries and following medical record review were discussed by the registry and study personnel, and changes made to either dataset as necessary.

3.1.3. Data Collection Process

We obtained information from the cancer registries about the patients' sex, age at diagnosis, date of initial diagnosis, name and address of the treating clinician at the time of the initial diagnosis, the hospital where the diagnosis was made (if applicable) and, where available, the date of death. The cancer registries also provided the statistical local area (SLA) in QLD or local government area (LGA) in NSW for the patients' residential locations.

Following cancer registry notification, the research nurses accessed medical records for each patient, commencing with the record from the facility where the diagnosis was made if possible. They abstracted detailed information about patient management from the medical record onto a standardised case report form (CRF) (Appendix D). Discharge summaries and correspondence were checked for evidence of referral to other centres for further management, and medical records at these centres were also reviewed. If limited details were available we sought information from the patient's local general practitioner to enable completion of the CRF, but we did not routinely ascertain details from general practice. Depending upon the number of centres visited by the patient and their treatment patterns, the time taken to complete a CRF varied from approximately 2 to 6 hours.

3.1.4. Data collected

Information collected on the case report form included details of:

(1) Initial presentation:

- symptoms
- investigations
- comorbidities
- resectability / clinical stage of disease.

(2) Treatment:

- whether or not surgery occurred, and if not, the reason why not
- if surgery occurred, the place of surgery and the surgeon (both coded for anonymity), surgical procedure performed (pancreaticoduodenectomy, total or distal pancreatectomy), surgical margins achieved and complications experienced
- chemotherapy and radiotherapy including planned regimens, dates and doses of drugs/radiation administered, complications and responses
- details about insertion of biliary stents or surgical bypass for obstructed bile duct
- symptom management, including prescription of replacement pancreatic enzymes, coeliac plexus blocks or use of opioids for pain management and treatment of nausea

(3) Referrals to:

- multidisciplinary team (including dates presented)
- social workers
- physiotherapists
- psychologists
- palliative care services
- dieticians
- nursing care coordinators

(4) Admissions occurring up until death or to 12 months after the index admission including:

- dates of admission and discharge,
- the types of health professionals involved in each episode of care
- all investigations and treatment.

(5) Patient's disease status at six and twelve months post diagnosis:

- if alive, place of residence
- if deceased, date and cause of death.

Cancer registries provided up-to-date survival status in February 2014.

3.1.5. Quality assurance

The research nurses who conducted the medical record reviews underwent an initial two-day training workshop with clinicians in attendance. This was repeated midway through the data collection period (after approximately 18 months). At these workshops, all nurses reviewed the same series of charts and completed CRFs. Completed CRFs were compared, with discrepancies discussed, and differences in interpretation resolved.

I (a registered nurse) commenced data collection following the training workshop and completed the training individually. My training involved completing a training CRF with reference to a working data collection manual. To ensure data quality I then completed CRFs for patient charts previously reviewed and the CRFs were audited. After completion of three chart reviews, discrepancies between reviews were less than 1%, and this was confirmed following a further two review audits.

3.1.6. Data management

Professional data entry staff entered information from the CRFs into a Microsoft Access database. We undertook a comprehensive series of range and logic checks to ensure the accuracy of the data. Data entry errors were corrected with reference to the original CRFs. Logic errors were corrected through consensus review by me, A/Prof Neale and the nurses who collected the data where possible. Notes that were taken during the review assisted with this process.

3.1.7. Candidate contribution to data collection

I joined the patterns-of-care pancreatic cancer group and commenced data collection in September 2012; I completed the final chart review in June 2013. During this time I reviewed approximately 350 charts for about 120 patients from 44 medical facilities throughout QLD, drove over 5000km and spent 17 nights away from home (Table 3-1). With the aid of a research assistant I completed the comprehensive data cleaning. I wrote the data checks and together we tested the quality of the data, amending the data as required.

Table 3-1 : Contribution of candidate EAB to data collection in Queensland

	NSW	QLD	EAB in QLD
Number of patient reviews	1052	811	±[a] 120 (15%)
Medical facilities visited	119	141	44 (31%)
Chart reviews		±[a] 2100	± 350[a] (17%)

Note: [a] Unable to calculate precise numbers as numerous charts may have been examined by different research nurses for each patient. Study registers only recorded the research nurse who began the initial chart review and the nurse who completed the final chart review.

3.1.8. Patterns-of-care study enrolment

NSW and QLD cancer registries notified the study team of 2090 potentially eligible patients for the patterns-of-care study (Figure 3-1). We accessed the records for 2003 (96%) of these and found 140 (7%) to be ineligible. Reasons for ineligibility are listed in Table 3-2. Of the 1863 eligible patients, we completed chart reviews for 1695 and 168 were partially completed.

Table 3-2: Reasons for patterns-of-care study ineligibility

Reason	**Number (%)**
Tumour did not originate in the pancreas	94 (67)
Tumour was not adenocarcinoma	23 (16)
Patient was not resident of NSW or QLD	18 (13)
Diagnosed outside study dates	5 (4)
Total	140

Reviews were not commenced for 87 patients due to difficulty accessing records or because the cancer registries were only notified when the patient died and no hospital information was available.

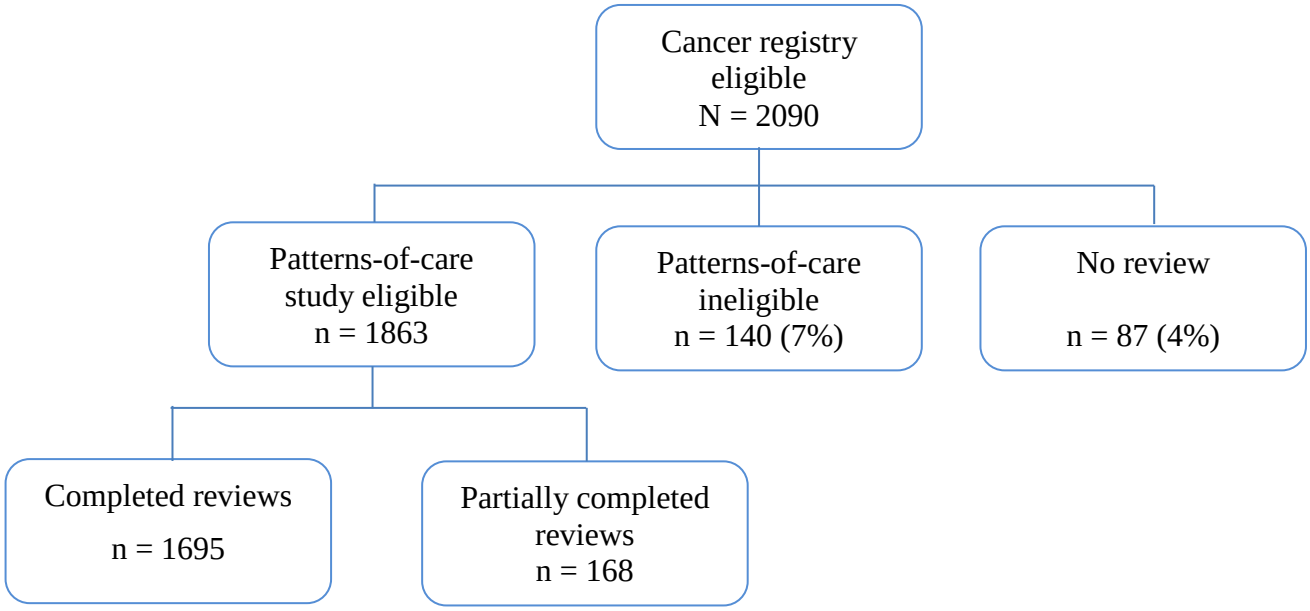


Figure 3-1: Patterns-of-care cancer registry notifications, eligibility and chart reviews

3.2. DEVELOPMENT OF THE QUALITY-OF-CARE SCORE

I designed and implemented an electronic Delphi process to develop a set of quality-of-care indicators. Patient care was then benchmarked against these to calculate an overall quality-of-care score for each patient.

I aimed to recruit a diverse range of clinicians involved in the care of patients with pancreatic cancer, including surgeons, gastroenterologists, oncologists, palliative care physicians, allied health professionals, interventional radiologists, general practitioners and nurses. I identified potential Delphi participants through searching the literature, personal contacts and professional groups involved in the care of pancreatic cancer patients across Australia. I also asked participants to nominate other relevant clinicians at the time they completed the survey. In total I identified 250 clinicians.

The Delphi survey was administered using a security-enhanced version of an electronic survey application (SurveyMonkey Inc.).[242] I emailed clinicians an invitation to participate, including the aims of the research and a link to the survey, which asked the clinicians to "list all/any factors you consider important in the care of patients with suspected or confirmed pancreatic cancer". This initial survey also included questions about specialty, number of years of experience in their specialty, the number of years caring for patients with pancreatic cancer, and age-group. Completion of the questionnaire was considered as consent to participate.

A/Prof Neale and I thematically analysed the list of 380 responses (from 78 participants) to the open-ended question to generate a list of 55 indicators. The statements were grouped into four sections which encompassed themes of presentation/staging, surgery and biliary obstruction, multidisciplinary team details and oncology. I then invited all 250 clinicians, irrespective of whether or not they had responded to the first survey, to complete an electronic survey in which they were asked to score each statement (indicator) on a scale from 1 (not at all important / strongly disagree) to 10 (extremely important / strongly agree). I also invited respondents to suggest amendments to the statements to improve content validity. Non-responders were re-sent the electronic survey in an attempt to increase participation. A total of 65 participants completed the first scoring round.

I calculated the mean score for each indicator and made amendments to the statements where feasible. I then sent the survey to all clinicians who had responded to either the open-ended question or the first survey, with the mean score for each of the original responses included. Participants were asked to re-score each item, after consideration of the group mean.

Overall 63 (66% of those sent the final questionnaire; 25% of those initially invited) health professionals from 9 disciplines completed the final scoring of the 55 statements. Mean scores ranged from 3.7 to 9.7 with the highest scores related to communication and patient assessment. There was substantial intra- and inter-disciplinary variation in views about multidisciplinary team membership and roles.

3.2.1. Calculating a quality-of-care score

A quality-of-care score for participants in the patterns-of-care study based on the indicators identified through the Delphi process was calculated. Only those indicators for which data had been collected from the medical records could be included, resulting in 18 indicators.

For each patient I identified a set of indicators specific to their clinical situation. For example, indicators related to surgical volume were only included in the indicator set for patients who underwent an attempted resection. The mean scores from the Delphi process for the relevant indicators were summed to create a total potential score for each participant. To create a total actual score I summed the scores for the relevant items where there was evidence in the medical record that the care had been delivered. This was divided by the potential score to create a proportional care score.

The formula was:

$$Si = \frac{\sum_{j=1}^{18} wj * xij * yij}{\sum_{j=1}^{18} wj * xij}$$

Where Si is the score for patient i (i = 1,…,n):

wj is the weight (the mean score from the Delphi process) for item j

For patient i:

xij indicates whether or not item j is applicable to patient i (xij = 1 or 0)

yij indicates whether item j was met for patient i (yij = 1 or 0)

The advantage of this approach for calculating the score is that it applied a relative weight depending on the importance that the expert panel attributed to each item. This is preferable to applying the same weight to all items which is an approach that has been used previously.[119, 168, 243] The distribution of the score for all patients, patients who underwent surgical resection of their tumour and patients with no surgical resection was examined and found to be normal in all groups.

3.3. ANALYSES

Analyses are described in detail in each results chapter; the approaches used are summarised briefly in this chapter. I used Stata13/14 (Statacorp, Texas) for all analyses.

Table 3-3 shows the definition and derivation of explanatory and outcome variables used in the analyses.

Table 3-3: Derivation of analysis variables and corresponding codes

Variable	Description
Patient characteristics	
Date of diagnosis	Earliest date from histological or imaging diagnosis.
Age at diagnosis	Age at diagnosis (as above) in years
Sex	As recorded by the cancer registries at diagnosis.
Performance status	Eastern Cooperative Oncology Group (ECOG) ranking at diagnosis. If not recorded in the medical record, derived from admission notes where possible.
Charlson comorbidity index.[244]	Comorbidities such as cardiovascular disease, respiratory disease, renal impairment, diabetes and other cancers were recorded as noted in patient medical records. These were then coded and the Charlson comorbidity index calculated by summing the number of comorbidities according to the Charlson scoring methods.[244] Total index scores were categorised into three groups: score equal to zero, score equal to one and score equal to two or more.
Socio-economic Index For Areas (SEIFA)[2]	Using the statistical local area for Queensland and the local government area for New South Wales, each patient was allocated an Index of Relative Socio-economic Disadvantage (IRSD) (SEIFA 2011)[245] score and ARIA[246] category according to their place of residence at diagnosis. The SEIFA scores were used to rank the patients' area of residence into quintiles of disadvantage by using the quintile cut-points for the state-specific population distributions. Place of residence (ARIA) categories were collapsed into three groups: major city; inner regional; and outer regional/remote/very remote.
Accessibility/ Remoteness Index of Australia (ARIA)[246]	
Tumour characteristics	
Site of tumour within the pancreas	The site of the tumour within the pancreas was categorised into four groups: (1) head/neck/uncinate process; (2) body; (3) tail; or (4) multiple/unstated. Obtained from clinical notes in the medical records, including radiological investigation reports.
Stage of tumour	Stage of the tumour was extracted from medical records, (multidisciplinary meeting notes, medical specialist notes, autopsy reports) radiology or pathology reports. Surgical specimen reports, where available, took precedence over biopsy reports. Where there was inadequate staging information in the notes, collaborating medical specialists reviewed investigations to clarify staging information, where possible. Two approaches to staging were recorded: (1) The final stage of the tumour, which incorporated findings at surgery, was classified using the TNM UICC staging system[81] and classified as stage I – IV disease. (2) Classified according to resectability of the tumour, as confined to the pancreas, locally advanced disease or metastatic disease and based on all staging investigations.
Resectable	The classification of the disease as resectable or not was obtained from clinical notes in the medical records.

Variable	Description
Health Service Characteristics	
Type of specialist first seen	The specialty of the first specialist seen by a patient on diagnosis, either following referral by the general practitioner or at a hospital.
Hepatobiliary surgeon	Defined as a surgeon with recognised specialised hepatobiliary surgical training and/or is recognised by their peers as an experienced hepatobiliary surgeon. Surgeons were coded for anonymity and each code was allocated to either a general or hepatobiliary surgeon. For surgeons where data collectors were uncertain of their specialty classification, details were forwarded to the hepatobiliary surgeon on the study management team to be classified.
Review by a multidisciplinary team (MDT)	If there were notes from any formal MDT meeting in the medical record the patient was recorded as having been presented to an MDT. They were otherwise classified as having no evidence of MDT review. There were no details of what constituted an MDT and in some smaller centres this was subjective. If there was evidence of a collaborative review by multiple clinicians in a formal or informal context this was classified as an MDT. For example, if a surgeon, palliative care specialist and oncologist or social worker had met to discuss the patient care plan this was classified as an MDT.
First facility of presentation	The first facility to which the patient was admitted. If not admitted then the facility to which they initially presented.
Volume of first facility	We used information from patients whose medical records were reviewed to code the volume of the first facility attended using two methods: (1) The number of pancreatic cancer resections performed each year by the facility. Initial categories were based on the literature but following sensitivity analyses and clinical judgement category cut-points of ≤ 4, 5 and ≥ 6 resections per year were used. This coding was used for surgical outcome analyses but was not suitable for whole cohort analyses as many patients did not undergo resection of their tumour. (2) The number of patients first admitted to a facility each year. Facilities categorised into three groups: < 10, 10 - 29 and ≥ 30 patients.
Volume of surgeon	This variable was used for the surgical outcome analyses only (Appendix H). The number of resections performed each year by a surgeon on eligible patterns-of-care study cases with medical records reviewed, with ≤ 4 resections per year classified as low volume, 5 medium and ≥ 6 as high volume.
Chemotherapy	Coded as received if a patient received any chemotherapy.
Surgery	Surgery was recorded as attempted if a laparotomy occurred and a pancreatic resection was planned but was unable to be completed for reasons such as vascular invasion or the presence of metastases. A surgical resection was recorded as complete if the pancreatic tumour was surgically removed, irrespective of the margin status.
Investigations	The date of each investigation performed was recorded. Investigations included: computerised tomography (CT) (+/- pancreas protocol), endoscopic ultrasound (EUS), endoscopic retrograde cholangio-pancreatography (ERCP), magnetic resonance imaging (MRI) or cholangiopancreatography (MRCP), and laparoscopy or laparotomy.

Descriptive statistics including frequencies and percentages were used to describe the cohort according to variables listed in Table 3-3. The proportions of patients for whom surgery was attempted or completed, and who received chemotherapy were estimated and expressed as percentages, and were included as outcomes or independent variables in the analyses.

3.3.1. Missing data

Cases with missing data were omitted from the denominators for the descriptive percentages. Complete-case analyses (only including cases with non-missing data) were performed, when missing data was found in the exposure or outcome variables. Only performance status (ECOG) at diagnosis had significant missing data (n=263, 14%). Results from complete-case analyses (only including cases with non-missing ECOG) were compared with those from all-case analyses (with the missing values coded as a separate category) and if a difference was noted with the inclusion of the missing category, missing values were included in multivariable analyses.

3.3.2. Survival

Survival time was calculated as the number of days between the date of diagnosis and death from any cause or, if no record of death was located, 25 February 2014 (date of final death status review). Survival curves and median survival were estimated using Kaplan-Meier methods. The median time of follow-up was estimated using reverse Kaplan-Meier methods.[247]

3.3.3. Statistical models

The associations between all patient, tumour and health-care factors and outcomes were tested using Chi-squared tests and logistic regression for binary outcomes (including mortality, attempted surgery, and classification as resectable disease), linear regression for continuous outcomes (quality-of-care score) or Cox proportional hazards models for survival. All model assumptions were checked prior to use. When the outcome of interest is a common event (occurring in >20% of patients in any group), it was recognised that odds ratios cannot be interpreted as a relative risk.

For multivariable causal models I used directed acyclic graphs to guide the selection of potential confounding variables to maximise control of confounding and avoid introducing bias.[248]

Hierarchical mixed effects models, with hospital as a random intercept, were used to adjust for the effects of clustering within hospitals when assessing associations between the outcomes of interest and hospital volume.

3.4. ETHICAL APPROVAL

For the patterns-of-care study, we accessed medical records without patient consent; approval for this access was obtained under the Queensland Public Health Act and under the guidelines of the New South Wales Privacy Act. Ethics approvals were obtained from the Human Research Ethics Committees at the QIMR Berghofer Medical Research Institute (P1292), the Royal Brisbane and Women's Hospital (on behalf of all public hospitals in Queensland) (HREC/10/QRBW/16) and by the New South Wales Population and Health Services Research Ethics Committee (HREC/10/CIPHS/45). Approximately 250 additional ethics approvals and/or individual site-specific approvals were obtained for each public hospital and private hospital as required.

Ethical approval from the QIMR Berghofer Medical Research Institute for the sub-study to develop the quality-of-care score was obtained, as an amendment to the patterns-of-care study.

The University of Queensland approved the research contained in this thesis: Ethics Approval EB020713.

Chapter 4: Development of a quality-of-care score

4.1. INTRODUCTION

The objective of the publication presented in this chapter was to establish components of care which Australian health professionals believed important in providing optimal care and management of patients with pancreatic cancer.

4.2. CONTRIBUTION OF CANDIDATE

All authors contributed to the conceptualisation of this publication, in particular Assoc. Prof. Rachel Neale. I contacted all Delphi participants (100%), designed the surveys (100%) collected and analysed all data (90%) with the aid of REN who completed an independent thematic analysis of the initial statements for quality and consistency purposes. I was responsible for writing (75%), editing (36%) and submitting (90%) the manuscript taking into account the comments and suggestions of REN and the study team.

4.3. MANUSCRIPT

The following work was published in the Asia Pacific Journal of Clinical Oncology:

Asia Pac J Clin Oncol 2016; 12 (2): 105-14.

Using a Delphi process to determine optimal care for patients with pancreatic cancer

Elizabeth A. Burmeister, Susan J. Jordan, Dianne L. O'Connell, Vanessa L. Beesley, David Goldstein, Helen M. Gooden, Monika Janda, Neil D. Merrett, David Wyld, Rachel E. Neale for The Pancreatic Cancer Clinical Working Group.

Authors have provided permission to include this publication in this thesis (Appendix I).

Abstract

Aim

Overall 5-year survival for pancreatic cancer is ~5%. Optimising the care that pancreatic cancer patients receive may be one way of improving outcomes. The objective of this study was to establish components of care which Australian health professionals believe important to optimally manage patients with pancreatic cancer.

Methods

Using a Delphi process, a multidisciplinary panel of 250 health professionals were invited to provide a list of factors they considered important for optimal care of pancreatic cancer patients. They were then asked to score and then rescore (from one (no importance/disagree) to 10 (very important/agree) the factors. The mean and coefficient of variation scores were calculated and categorised into three levels of importance.

Results

Overall 63 (66% of those sent the final questionnaire; 25% of those initially invited) health professionals from 9 disciplines completed the final scoring of 55 statements/factors encompassing themes of presentation/staging, surgery and biliary obstruction, multidisciplinary team details and oncology. Mean scores ranged from 3.7 to 9.7 with the highest related to communication and patient assessment. There was substantial intra- and inter- disciplinary variation in views about MDT membership and roles.

Conclusion

Overall the opinions of Australian health professionals reflect international guideline recommended care; however they identified a number of additional factors focusing on where patients should be treated, the importance of clear communication and the need for multidisciplinary care which were not included in current clinical practice guidelines. Differences in priorities between specialty groups were also identified.

Introduction

Pancreatic cancer is the 10th most commonly diagnosed cancer in more developed regions of the world. In Australia it is the 6th most common cancer diagnosis and the 4th leading cause of cancer related death.[249] People diagnosed with pancreatic cancer have the poorest prognosis of any cancer. One-year survival is currently 15% and five-year all-stage survival for pancreatic cancer in Australia is 5.2%, which mirrors other western countries.[36, 37] Current projections suggest that it will be the second leading cause of cancer death within 10 years as survival from other cancers improves.[40, 250]

Provision of optimal care increases the likelihood of desired health outcomes.[251, 252] To facilitate this clinical practice guidelines/recommendations for pancreatic cancer have been published in Europe[4, 5, 105, 188] and the United States.[6] However, the extent to which health professionals in the field agree with the guidelines, and if they consider all elements of the guidelines equally important

is not known. In addition, guidelines may not cover some clinical situations or aspects of care that health professionals believe to be necessary for optimal management.[253] Assessing the elements of care that specialist clinicians consider to be important for patients with pancreatic cancer and assessing whether these elements are evidence-based could assist in the modification of guidelines and/or identify areas where system changes or clinician education could help to improve patient outcomes.

One way of harnessing the opinions of a group of specialists is to use a Delphi process. This method has been used facilitate clinical consensus in a variety of medical situations.[232, 254, 255] It begins with open-ended questions soliciting information from a panel of experts in the field.[256] This is followed by ranking or scoring of the derived statements by the panel according to set criteria. The combined resultant scores/rankings are fed back to the panel members who are then invited to re-score the statements. The process is conducted anonymously, preventing domination of individuals and iterations of the scoring and feedback process repeated until consensus is reached or negligible change in scores is noted.

The aim of this study was to use a Delphi process to establish components of care which Australian health professionals believe are important to optimally manage patients diagnosed with pancreatic cancer.

Methods

The Delphi process

We used the literature, personal contacts and professional groups, including the Australian Pancreatic Cancer Genome Initiative[257] and Cancer Council Australia, to identify health professionals involved in the care of pancreatic cancer patients from across Australia. We emailed these clinicians inviting them to participate and also asked them to nominate other clinicians who may be interested in participating. The panel consisted of surgeons, medical oncologists, radiation oncologists, gastroenterologists, palliative care specialists, nurses, allied health professionals, interventional radiologists and general practitioners. These experts were initially asked (online) to "...list all/any factors you consider important in the care of patients with suspected or confirmed pancreatic cancer." They were also asked about their specialty and years in practice.

The responses to the open-ended question were used to develop the quantitative questionnaire. Each response was grouped with those of similar themes and we eliminated duplicate statements. This process was done independently by two authors (EB and RN) and a structured list of

statements was developed. Where possible, statements were used as written by participants. Some statements with similar inferences required merging to avoid duplication; these were discussed within the study team to avoid corrupting their original meanings.

Via email, we invited panel members to complete the quantitative questionnaire. They were asked to rate the importance of, or their level of agreement with, each statement on a scale of one (no importance/disagree) to 10 (very important/agree). Panel members could record 'no opinion' for statements they felt were beyond their scope of expertise. We provided the mean and median scores for each statement from the initial questionnaire to those who had responded to either the open-ended question or the first quantitative questionnaire and asked them to re-score the statements in light of this information.

Analyses

The mean and coefficient of variation (CV) were calculated for each statement using the scores for all participants and also stratified according to specialty. The CV is the ratio of the standard deviation (SD) to the mean and gives the relative magnitude of the SD; it was multiplied by 10 for ease of reporting.

Using a priori criteria each statement was categorized based on the mean score and CV as follows:

Mean 9 - 10; CV < 4: very important

Mean 6 – 8.9; CV < 4: moderately important

Mean 1- 5.9; CV < 4: unimportant

Any mean; CV ≥ 4: unable to agree.

We used analyses of variance (ANOVA) to assess differences between the specialty groups.

Ethics

The Human Research Ethics Committees of the QIMR Berghofer Medical Research Institute and the University of Queensland approved this study. Completion of questionnaires was considered to imply consent.

Results

In June 2013, 250 health professionals involved in the care of pancreatic cancer patients were invited by email to complete the initial open-ended question (Figure 4-1). Of these, 78 (31%) replied and suggested a total of 380 overlapping items that they considered important in the care of

pancreatic cancer patients. These were reduced to 55 items that encompassed the following themes: presentation and staging; surgery and biliary obstruction; the management team (including multidisciplinary team (MDT) details); oncology; and other (such as enrolling patients in clinical trials and establishing a national pancreatic cancer prospective database). The list of 55 items was then sent to the original 250 health professionals, irrespective of whether or not they responded to the first open-ended question. Following scoring of the initial items, the statements were resent to the 96 health professionals who had responded during round 1 or round 2. Of these, 63 (66% of those sent the final questionnaire; 25% of those initially invited) rescored the items.

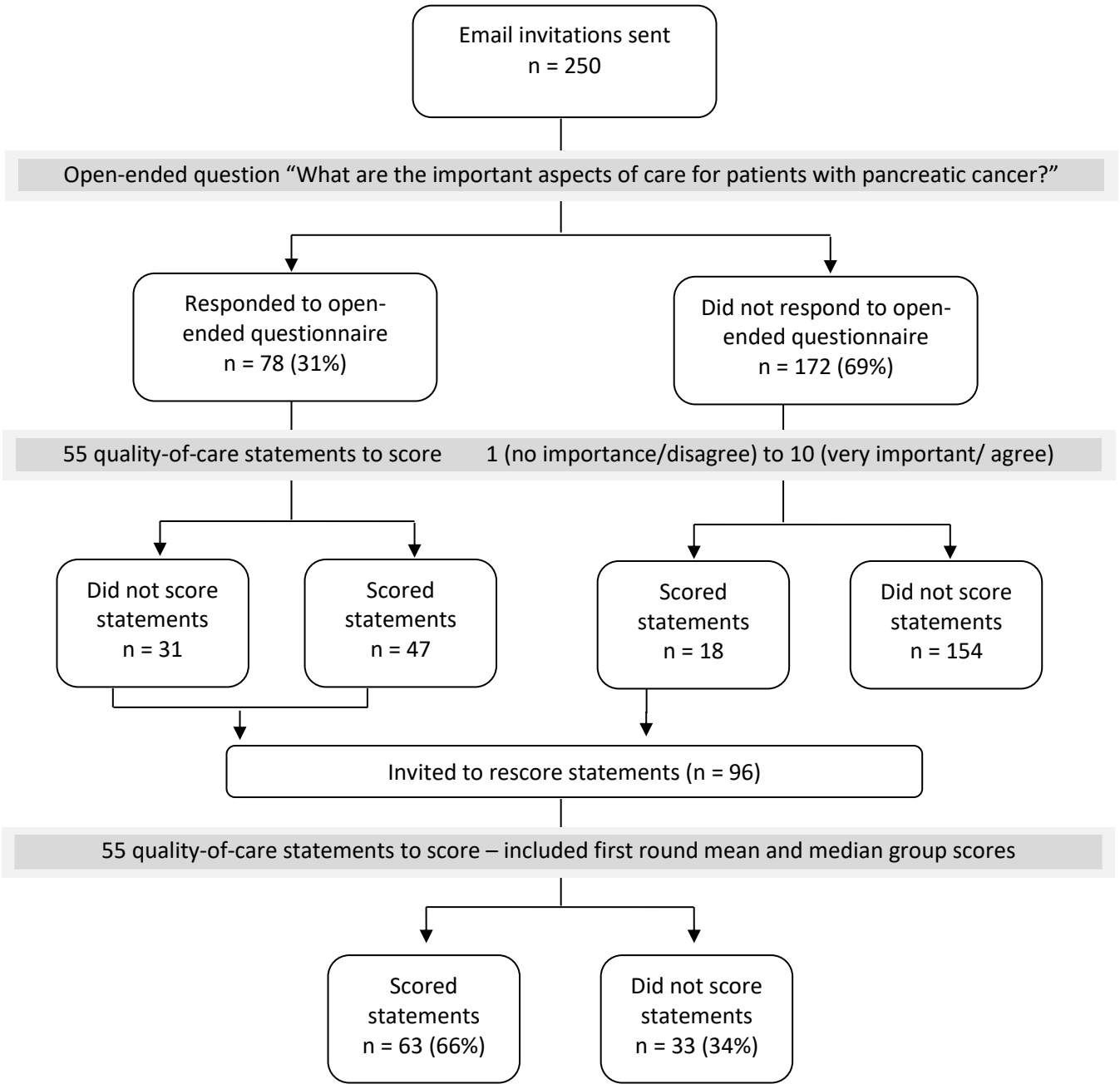


Figure 4-1: Consort diagram for the number of health professionals participating in the modified Delphi process

Specialties of the participants invited included surgery (n = 56; 22%), medical oncology (n = 43; 17%), allied health and nursing (n = 40; 16%), gastroenterology (n = 29; 12%), palliative care (n = 28; 11%), radiation oncology (n = 13; 5%), and others (n = 41; 16%) which included interventional radiology, general practice, gerontology and medicine (Figure 4-2). The response proportion to the final questionnaire ranged from 10% (other) to 54% (radiation oncology). The specialties of the

final questionnaire respondents were: 22% - medical oncology, 18% - surgery, 19% - palliative care, 18% - allied health and nursing, 11% - radiation oncology and 6% from each of gastroenterology and others. Seventy-six respondents to the initial open-ended questionnaire (97%) described their clinical experience. Of these 12, (16%) reported more than 20 years treating patients with pancreatic cancer and treating more than ten patients each year. The majority of respondents treated more than 10 patients each year (n = 43, 57%) and years of experience were reported as less than 10 years, 10 to 20 years and more than 20 years by 30 (39%), 25 (33%) and 21 (28%) clinicians respectively.

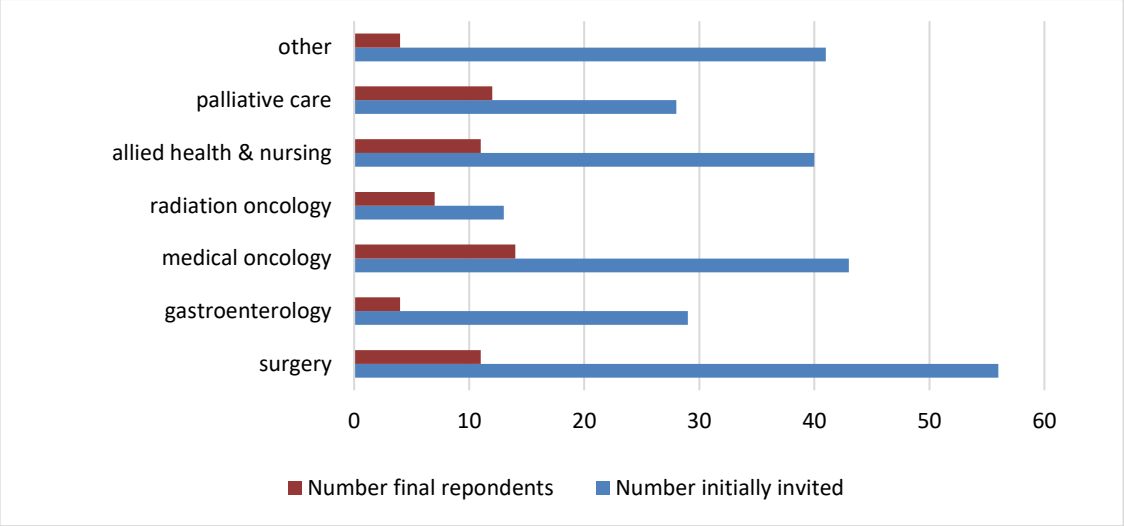


Figure 4-2: Numbers of invited and final responders by specialty

Based on the initial scores, 8 of the 55 statements (15%) were classified as very important and 33 (60%) as moderately important. The CV was greater than 4 for 14 (25%) statements, including 8 that were considered unimportant. No items where the CV was less than 4 were classified as unimportant. Only two statements "All patients should have a full physical examination, geriatric assessment if elderly, assessment of comorbidities and performance status prior to any treatment" and "Patients should be fully aware of the risks and benefit of interventions prior to any treatment" were given a moderately-high or higher score by all participants.

The mean scores for almost half the statements (n = 24; 44%) increased between surveys but were unchanged for 17 statements (31%), and decreased for 14 (25%) statements. The majority (n = 30; 55%) of CVs remained the same between surveys; 11% (n = 6) increased and 35% (n = 19) decreased between surveys.

Statements scores according to clinician specialty are displayed below within thematic categories and by score of importance (Table 4-1).

Table 4-1: Final scores for all statements by specialty

		Surgery	Gastro-enterology	Medical Oncology	Radiation Oncology	Allied Health & Nursing	Palliative Care	Other	Total
	n†	Mean (Coefficient of Variation)							
Presentation and Staging (n = 13 statements)									
[a]All patients should have a full physical examination, geriatric assessment if elderly, assessment of comorbidities and performance status prior to any treatment	59	8.9 (2)	10.0 (0)	9.2 (1)	9.1 (1)	9.0 (2)	9.3 (2)	8.8 (2)	9.2 (2)
[a]Standard guidelines for staging should be developed	60	8.5 (3)	10.0 (0)	9.4 (1)	9.1 (1)	9.3 (1)	8.6 (2)	8.8 (2)	9.1 (2)
[b]All patients should have a triple phase/ pancreas protocol CT scan for staging	55	9.5 (1)	10.0 (0)	8.9 (1)	9.0 (1)	9.3 (1)	7.6 (4)	8.5 (2)	8.9 (2)
[b]All patients should have an initial TNM stage recorded	59	7.9 (3)	10.0 (0)	9.1 (1)	8.6 (2)	9.1 (1)	8.4 (2)	8.3 (2)	8.7 (2)
[b]Standard guidelines should be developed to determine which patients would benefit from transfer to a tertiary centre	61	8.2(2)	10.0 (0)	7.7 (3)	9.0 (1)	8.5 (2)	8.7 (2)	6.5 (2)	8.3 (2)*
[b]Tissue diagnosis should be obtained where possible	59	7.2 (3)	6.2 (8)	8.9 (2)	9.1 (1)	8.9 (2)	8.3 (2)	8.3 (2)	8.3 (3)
[b]All patients should have access to ERCP and EUS facilities	57	7.4 (3)	10.0 (0)	8.2 (2)	7.9 (2)	9.2 (1)	7.8 (3)	7.8 (3)	8.2 (2)
[b]A laparoscopy should be performed if resectability is uncertain	52	7.1 (4)	9.5 (1)	8.0 (3)	8.7 (1)	8.0 (1)	7.9 (2)	6.8 (2)	7.9 (2)
[b]All patients presenting with ongoing epigastric/back pain should have a CT as part of the initial investigations	58	8.0 (3)	8.0 (4)	7.6 (3)	7.7 (1)	8.2 (2)	8.5 (1)	6.0 (2)	7.8 (2)
[b]General practitioners should coordinate the initial workup	59	7.3 (2)	7.0 (3)	6.4 (3)	5.9 (4)	7.1 (4)	7.2 (3)	7.3 (2)	6.8 (3)
[c]If disease appears to be localised a PET scan should be performed	56	5.1 (4)	8.4 (3)	6.1 (5)	7.7 (2)	7.4 (3)	8.4 (2)	6.8 (3)	6.9 (4)*
[c]All patients should have an EUS	56	6.2 (5)	6.6 (6)	6.4 (3)	5.4 (4)	7.2 (3)	5.5 (4)	5.0 (6)	6.1 (4)
[c]All patients presenting with ongoing epigastric or back pain should have a CA19.9 blood test	56	5.9 (6)	4.0 (8)	4.6 (7)	4.3 (6)	5.3 (2)	5.3 (4)	4.5 (1)	4.9 (6)
Surgery and biliary obstruction (n = 9 statements)									
[a]All patients with a small lesion and technically resectable disease plus adequate performance status should be offered a resection	57	9.2 (1)	10.0 (0)	9.1 (1)	9.3 (1)	10.0 (0)	8.8 (1)	8.7 (2)	9.2 (1)
[a]Resectability should be assessed and surgery performed by surgeons who perform more than 5 pancreatic surgeries per year	53	8.7 (2)	10.0 (0)	8.7 (2)	9.3 (1)	9.2 (2)	8.8 (1)	8.5 (2)	9.0 (2)
[b]Surgery should take place in tertiary institutions where > 15 resections are performed annually	57	7.5 (4)	10.0 (0)	8.4 (2)	9.0 (1)	9.4 (2)	8.5 (2)	8.5 (2)	8.6 (2)
[b]Biliary obstruction should routinely be managed endoscopically in non-resectable patients	50	8.2 (3)	9.0 (2)	8.6 (1)	8.4 (1)	8.3 (1)	7.5 (2)	8.0 (2)	8.2 (2)
[c]Patients with resectable disease should not be stented prior to surgery unless surgery is delayed	42	5.7 (5)	9.6 (1)	5.6 (5)	7.5 (2)	9.0 (0)	7.1 (3)	7.0 (0)	6.8 (4)

		Surgery	Gastro-enterology	Medical Oncology	Radiation Oncology	Allied Health & Nursing	Palliative Care	Other	Total
	n†	Mean (Coefficient of Variation)							
[c]A self-expandable metallic stent (SEMS) should be used instead of a plastic stent if biliary drainage is indicated prior to surgery	36	5.7 (6)	7.2 (5)	6.9 (3)	6.5 (2)	9.0(-)	6.8 (3)	5.5 (1)	6.6 (4)
[c]Potential for coeliac plexus block should be discussed before any surgical procedure	41	3.3 (6)	6.6 (5)	5.9 (4)	5.5 (6)	9.0 (-)	7.2 (2)	7.0 (-)	5.8 (5)*
[c]Biliary obstruction should be managed surgically if performance status and prognosis are satisfactory in non-resectable patients	48	5.2 (4)	2.2 (8)	4.5 (3)	4.8 (3)	5.5 (1)	5.7 (4)	6.0 (5)	4.8 (4)
[c]Potentially resectable patients should not have a tissue biopsy prior to surgery	46	5.3 (5)	3.6 (11)	4.5 (5)	3.4 (4)	4.5 (2)	5.3 (4)	6.0 (5)	4.7 (5)
Oncology and Other (n = 14 statements)									
[a]Patients should be fully aware of the risks and benefit of interventions prior to any treatment	63	9.6 (1)	10.0 (0)	9.7 (1)	9.0 (2)	10.0(0)	9.7 (1)	9.3 (1)	9.7 (1)
[a]Patients should be advised of the limitations of chemotherapy	61	9.5 (1)	10.0 (0)	9.5 (1)	9.1 (1)	9.9 (0)	9.6 (1)	9.0 (2)	9.5 (1)
[a]Careful attention to pain control is important, using nerve blocks if required	58	8.3 (2)	10.0 (0)	9.1 (1)	9.1 (1)	9.9 (0)	9.6 (1)	9.3 (1)	9.3 (1)*
[b]All patients should have a collaborative generalist/ specialist care model	61	7.4 (4)	9.0 (2)	8.7 (1)	9.0 (1)	9.9 (0)	9.3 (1)	8.8 (1)	8.8 (2)*
[b]Entry into a clinical trial should be considered for all patients	57	7.7 (3)	8.8 (2)	9.4 (1)	9.1 (1)	9.5 (1)	8.3 (3)	8.3 (2)	8.8 (2)
[b]Apart from surgery, all treatment should occur as close to the patient's home as possible	62	9.3 (1)	9.8 (0)	8.7 (2)	7.1 (3)	9.7 (1)	8.7 (3)	7.3 (4)	8.8 (2)*
[b]All pancreatic cancer patients' details should be entered into a prospective database	60	9.1 (2)	9.8 (0)	8.4 (2)	8.7 (1)	8.7 (2)	8.3 (2)	8.0 (2)	8.7 (2)
[b]Tissue should be routinely banked	51	9.2 (1)	9.2 (1)	8.9 (1)	6.8 (5)	9.8 (1)	7.1 (4)	9.0 (1)	8.5 (2)*
[b]All patients should be offered adjuvant therapy post operatively, assuming performance status is adequate	52	7.7 (4)	8.0 (3)	9.0 (1)	7.9 (2)	9.3 (1)	7.5 (2)	7.5 (1)	8.1 (2)
[b]Creon prescription should be considered for all patients	51	9.0 (1)	6.2 (5)	8.0 (2)	6.8 (4)	8.8 (1)	7.9 (2)	6.5 (3)	7.9 (3)
[b]All patients should have access to new drugs	59	7.2 (3)	8.2 (2)	7.9 (2)	7.7 (3)	8.9 (2)	7.2 (3)	7.5 (2)	7.7 (3)
[b]Borderline resectable cases should be considered for neo-adjuvant therapy	51	6.8 (4)	8.8 (1)	6.9 (3)	8.0 (2)	9.0 (1)	7.3 (2)	8.0 (0)	7.5 (3)
[b]Biomarkers should be used as prognosis and management tools	51	7.7 (3)	7.8 (4)	7.4 (3)	7.2 (3)	8.7 (1)	6.6 (3)	8.5 (2)	7.4 (3)
[b]All patients should have access to conformal radiotherapy	52	6.2 (3)	8.3 (3)	6.6 (4)	8.9 (1)	7.5 (3)	7.5 (2)	7.0 (0)	7.2 (3)

		Surgery	Gastro-enterology	Medical Oncology	Radiation Oncology	Allied Health & Nursing	Palliative Care	Other	Total
	n†	Mean (Coefficient of Variation)							
MDT and Referrals (n = 19 statements)									
[a]All patients with potentially resectable disease should be referred to an hepato-biliary surgeon	59	9.9 (0)	8.2 (5)	9.6 (1)	9.7 (1)	10.0 (0)	8.7 (2)	7.8 (3)	9.3 (2)
[a]Tumour resectability should be assessed by a MDT at a tertiary hospital	60	8.4 (2)	10.0 (0)	9.3 (1)	9.1 (1)	9.6 (1)	8.4 (1)	7.7 (3)	9.0 (1)*
[b]MDT meetings should include palliative care specialists	63	8.5 (2)	7.2 (4)	8.2 (2)	8.9 (1)	9.6 (1)	9.3 (2)	9.0 (1)	8.7 (2)
[b]Symptom management should be discussed at MDT meetings	63	6.8 (4)	9.0 (2)	7.7 (3)	8.9 (1)	9.5 (1)	9.2 (1)	8.8 (1)	8.5 (2)*
[b]Each patient should have a care-coordinator assigned with an individualised treatment/ clinical plan	62	7.8 (2)	9.6 (1)	8.2 (2)	8.7 (1)	9.5 (1)	8.3 (1)	8.0 (3)	8.5 (2)
[b]Tertiary hospital MDTs should be involved in the care of patients from smaller centres (via video-conferencing etc if necessary)	62	8.9 (1)	10.0 (0)	7.8 (2)	8.9 (1)	9.4 (1)	8.1(2)	7.3 (2)	8.5 (2)*
[b]MDT meetings should include allied health professionals	61	7.4 (4)	9.0 (1)	7.8 (3)	8.7 (1)	9.1 (2)	8.8 (1)	9.0 (1)	8.4 (2)
[b]All patients should be presented to a MDT	63	7.1 (5)	10.0 (0)	8.1 (2)	8.9 (1)	9.7 (1)	7.3 (4)	7.3 (1)	8.3 (3)*
[b]Patients requiring diabetes management should be seen by a diabetic educator	63	7.8 (3)	9.4 (1)	8.8 (1)	7.6 (2)	9.1 (1)	7.3 (3)	8.3 (2)	8.3 (2)*
[a]All patients should be offered psychosocial support	62	6.7 (3)	9.4 (1)	8.0 (3)	6.7 (3)	8.8 (3)	8.6 (2)	7.8 (3)	8.0 (3)
[b]All patients should see a medical oncologist	58	8.2 (3)	7.6 (4)	8.1 (2)	8.0 (2)	8.3 (4)	7.2 (4)	7.8 (3)	7.9 (3)
[b]A specialist HPB surgeon should be the initial/primary specialist unless the patient has obvious metastases	57	7.7 (3)	7.6 (3)	7.6 (2)	6.6 (4)	8.1 (3)	6.4 (3)	7.3 (3)	7.3 (3)
[b]All patients should be referred to a dietitian soon after diagnosis	61	6.5 (3)	8.2 (4)	7.9 (2)	7.1 (1)	7.8 (4)	7.0 (2)	6.3 (2)	7.3 (3)
[c]All patients should be referred to a social worker	60	5.9 (4)	7.0 (4)	6.4 (4)	5.0 (3)	6.9 (5)	6.6 (2)	7.3 (3)	6.4 (4)
[c]All patients should be referred to a physiotherapist	60	4.9 (6)	4.3 (5)	5.1 (4)	3.8 (3)	5.1 (4)	4.9 (5)	5.0 (3)	4.8 (4)
[c]All patients should be referred to an occupational therapist	59	4.3 (7)	5.8 (7)	4.8 (5)	4.7 (4)	4.1 (5)	5.3 (4)	4.8 (2)	4.7 (5)
[c]Patients should only be referred to palliative care when they have confirmed metastatic disease	59	6.7 (3)	4.2 (8)	5.4 (4)	6.5 (2)	7.1 (4)	5.5 (5)	7.0 (3)	6.0 (4)
[c]Only patients who are potentially suitable for resection should be presented to a MDT	61	5.1 (7)	1.2 (4)	4.3 (6)	2.0 (5)	1.8 (7)	4.3 (5)	4.8 (4)	3.6 (7)*
[c]On diagnosis all patients should be referred to palliative care	61	2.7 (10)	2.8 (8)	3.6 (5)	3.1 (5)	4.6 (6)	6.1 (5)	4.3 (7)	4.0 (6)*

CV = coefficient of variation PET = Positron emission tomography; EUS = Endoscopic Ultrasound; MDT = Multidisciplinary team; "Other" specialty group includes interventional radiologists, general practitioners and physicians.

[a] all agree important (9 +); [b] all agree moderately important (6 - 8.9); [c] unable to agree (CV ≥4); † Number of observations/respondents with an opinion;

* statistically significant (p-value less than 0.05) difference between groups.

Presentation and Staging:

Almost 25% of the statements derived from the initial open-ended question related to presentation and staging (n = 13; 24%). The need to conduct a full physical assessment prior to treatment and to develop standard staging guidelines were both rated as very important. The panel did not reach consensus about the value of positron electron tomography (PET) scans, endoscopic ultrasounds (EUS) or carbohydrate antigen 19.9 (CA19.9) as staging tools, with evidence of variability in the rated importance of these statements both between and within specialty groups. Palliative care specialists rated the value of PET scans more highly than surgeons (mean scores 8.4 and 5.1 respectively, p = 0.03) and had a lower CV (2 versus 4).

Surgery and biliary obstruction:

The 9 statements related to surgery and biliary obstruction had the fewest responses with some high proportions (9 – 91%) of the allied health, nursing and "other" groups indicating no opinion due to lack of expertise in the area. Amongst those who did respond, the statements "all patients with a small lesion and technically resectable disease plus adequate performance status should be offered a resection" and "Resectability should be assessed and surgery performed by surgeons who perform more than 5 pancreatic surgeries per year", were classified as very important. Consensus was not reached for 5 statements. Allied health /nursing and palliative care specialists rated the statement "Potential for coeliac plexus block should be discussed before any surgical procedure" much higher than the surgical specialists (scores 9.0, 7.2 and 3.3 respectively, p = 0.02).

Referrals and Multidisciplinary team (MDT):

Over a third of the survey statements (n = 19; 35%) referred to when and where treatment should occur, and which specialists should be involved. The statements "all patients with potentially resectable disease should be referred to a hepato-biliary surgeon" and "tumour resectability should be assessed by a MDT at a tertiary hospital" were thought very important with overall mean scores of 9.3 and 9.0 respectively.

No overall or within-specialty consensus was reached for the statement "On diagnosis all patients should be referred to palliative care" (CV = 6). There was a significant difference in the scores between palliative care and surgical specialists with mean scores of 6.1 and 2.7 respectively, (p = 0.03). Similarly, the panel did not agree on which patients should be presented at MDT meetings, with high inter- and intra-specialty variability.

Although surgeons and gastroenterologists had significant variation within their specialty groups (p < 0.001) they thought it less important that "MDT meetings should include palliative care

specialists" and that "symptom management should be discussed at an MDT" than allied health, nursing and palliative care specialists (p = 0.02).

Oncology and Others:

All the 14 oncology and "other" statements were classified as moderately or very important with participants able to reach consensus and ranking none as unimportant.

The statements that "patients should be fully aware of risks and benefits of interventions prior to any treatment" and "patients should be advised of the limitations of chemotherapy" were the highest scoring statements with total mean scores of 9.7 and 9.5 respectively and little variability across specialty.

Radiation oncologists regarded access to conformal radiotherapy as more important than other health professionals. Surgeons scored the statement "all patients should have a collaborative generalist/specialist care model" lower than all other health professional groups. This difference between surgical and allied health/nursing specialists was statistically significant (p = 0.03).

Gastroenterology, palliative care and allied health and nursing specialists rated the statement "careful attention to pain control is important, using nerve blocks if required" more highly than surgeons (p = 0.03).

Discussion

We used a Delphi process to identify factors that health professionals from a range of disciplines consider important in the care of patients with pancreatic cancer. As expected, many of the items rated as important are consistent with existing evidence-based clinical guidelines, but there were also items rated as important by health professionals that are not considered by guidelines. Furthermore, for some consensus-based or expert opinion-based items included in guidelines agreement on the importance of these between the health professionals we surveyed was not reached. We also found that the rating of particular issues varied substantially by clinical discipline.

Clinical guidelines have been developed by peak bodies in Europe and the United States, most notably the National Comprehensive Cancer Network (NCCN)[6] and the European Society for Medical Oncology (ESMO),[105, 188] which describe clinical pathways from diagnosis to treatment for patients with pancreatic cancer. In Australia no national clinical practice guidelines have been developed that are specific to the care of patients with pancreatic cancer.

Comparing current guidelines with the opinions of clinicians working in the field identified some areas requiring further clarification, in particular the diagnosis and staging of pancreatic cancer.

Respondents in this study rated highly the need for development of standard guidelines for staging. This was underscored by the very high variability in responses about the value of PET, CA19.9 and EUS. Lack of clarity about PET is also apparent in the guidelines, with NCCN stating that it is unclear if PET is useful and ESMO guidelines recommending PET not be used. Both organisations recommend that CA19.9 should only be used in treatment monitoring and that EUS be used as an adjunct to a pancreatic protocol computerised tomography (CT) or magnetic resonance imaging (MRI) only in those without biopsy-proven metastases. The high variation in scores for EUS amongst our participants may result from the inclusion of the words "all patients" in the statement as those with confirmed metastases would not benefit from the procedure.

It is notable that of the 55 items derived from panel members' responses, approximately half related in some way to access to treatment, where treatment should occur or who should be involved in different treatment aspects. This may be a recognition that pancreatic cancer patients require highly specialised care and the provision of treatment at specialist centres might improve outcomes. This could also reflect the substantial geographical dispersion of the Australian population and the finding of a trend towards poorer survival in rural and remote areas.[258] The study participants agreed that patients should be managed as close to home as possible, but that standard guidelines should be developed to determine who would benefit from transfer to a tertiary centre. Improved access through video-link to tertiary centres was also considered important. Telehealth aims to remove barriers to accessing medical services for residents of rural and remote Australia,[259] and there are International and Australian recommendations around its use.[260] The Queensland state Department of Health estimates that use of Telehealth would reduce health costs by 30% [261] and is currently under-used throughout QLD.[262]

Access to specialist surgical management was particularly highlighted. There was high agreement that all patients with potentially resectable disease should be assessed by a hepatobiliary surgeon, ideally as part of a multidisciplinary team. The need for multidisciplinary assessment of resectability is specifically stated in guidelines[6] and has been shown to improve surgical mortality rates[140] but it is unclear to what extent this currently occurs. Respondents also agreed that pancreatic cancer resections should occur in high-volume centres, reflecting guideline recommendations although definitions of high-volume vary across guidelines. The cut-off recommended by our panellists was consistent with the NCCN guidelines (15 surgeries/year). However, the National Cancer Institute (NCI) guidelines classify hospitals carrying out > 5 resections/year as high-volume and the British Society of Gastroenterology (BSG) guidelines[137] do not give a value, but rather recommend that surgery be carried out in 'specialist centres'. The evidence available suggests different values (range 5 - 19) for high-volume classification.[120, 128] Few data support a role for surgeon volume independent

of hospital volume,[128, 135] probably because these are highly correlated, but our participants nevertheless felt pancreatic resections should be undertaken by surgeons performing more than 5 per year. These data clearly show that clinicians feel that centralisation of surgical care for pancreatic cancer is important. In the United States, hospital volume for pancreatectomies more than tripled between 2000 and 2008 with the median volume increasing from 5 to 16[120] whereas in Australia volume is increasing but resections are still performed in low-volume hospitals.[100, 141]

Multidisciplinary care has become the accepted standard for cancer patients and has been shown to improve treatment access and timeliness.[252 263] However, systematic review evidence suggests there is substantial variability in the way MDT meetings are incorporated into patient care[170] and this is reflected in our data, which show that clinicians value multidisciplinary care but vary in their views about the function of MDTs in the management of patients with pancreatic cancer. For example, in contrast to other specialties, surgeons were less likely to agree that all patients should be presented to MDTs and more likely to indicate that only potentially resectable patients should be presented to MDTs. The NCCN guideline also suggests that only patients without metastatic disease be presented at MDT meetings. However, The European Partnership for Action Against Cancer (EPAAC) recommend in their MDT policy document[94] that MDTs co-ordinate cancer care at all stages. While there was strong consensus among our panellists across all specialties that palliative care specialists should be present at MDT meetings, the presence of allied health professionals was not consistently rated as important by surgeons. This may reflect the fact that surgeons lead most MDT meetings and may prioritise surgical and medical issues over psychosocial concerns.[185] EPAAC guidelines emphasise the need for MDTs to address the supportive care and psychosocial needs of their patients. They also emphasise the need for coordination across different disciplines to achieve continuity of care. While our Delphi process identified the importance of care coordination, the reality is that in Australia there is considerable variability in the way that the coordination role is implemented.[264] Adopting system-wide policies regarding MDTs and care coordination may be one way of improving the management of patients with pancreatic cancer.

The two top-scoring items in our study related to patient communication. Both items emphasised the importance of ensuring that patients are aware of the risks, benefits and limitations of treatment. While this should be standard in all clinical situations, it is particularly important for patients with pancreatic cancer where surgery can result in significant morbidity and, even with successful resection, median survival is poor at ~20 months.[265] In addition, current chemotherapy regimens have limited survival benefit and a United States national cohort study showed that about three quarters (69 - 81%) of patients with advanced cancer did not understand that the chemotherapy they were receiving was unlikely to result in cure.[266]

Up to 75% of patients with advanced pancreatic cancer report pain and it is one of the major factors adversely affecting quality of life.[207, 267, 268] The need to manage pain was one of the highest-scoring items on the survey, but there was a lack of consensus about whether coeliac plexus neurolysis (CPN) should be discussed before embarking on any surgical procedure. CPN can prevent pain development for up to 6 months post-operatively[269] and, while some studies suggest that CPN may not offer greater pain relief over opioid analgesia, it has fewer side effects.[268] The NCCN guidelines do suggest that CPN should be considered at the time of palliative surgery.

A major strength of this study was the robust method we used to elicit opinions from experts in pancreatic cancer management.[237, 270] Key features of the Delphi process we used included: (1) the multidisciplinary panel drawn from a wide range of medical and allied health fields; (2) each health professional rated the quality-of-care statements anonymously, limiting the potential for a single individual to dominate the proceedings; (3) we provided structured feedback, where following the first round of ratings the panel received the ratings from the entire group; (4) it was iterative, with two rating rounds allowing panel members to change their minds after deliberation;[255] (5) it was internet-based and therefore less costly than other methods such as focus groups.

The study has two key limitations. Firstly, although a broad range of specialist clinicians participated, response rates were highly variable and some specialties (notably gastroenterology) were under-represented. For ethical reasons we were unable to capture detailed information about the non-responders so it is difficult to determine the representativeness of the final sample in terms of factors such as location of practice and years of experience. Secondly, some statements did not fully portray the clinical variability that underlies decisions about care. This particularly applies to those statements which commenced with the words "All patients". While the statements had been transcribed verbatim following responses to the open-ended questionnaire and to amend them would have resulted in a deviation from the Delphi method, some items may have scored more consistently had they been worded differently.

This work shows that, for the most part, clinicians' opinions reflect clinical guideline-recommended care, albeit with some exceptions. However, clinicians identified a number of additional factors that are not incorporated in pancreatic-cancer specific guidelines, with a particular focus on where patients should be treated, the importance of clear communication and the need for multidisciplinary care. The lack of agreement about which patients and clinicians should be included in MDT meetings reinforces the notion that further in-depth investigations are required to identify the optimal composition and schedule of MDT meetings to improve and standardise practice in this area. Similarly, clinicians support the need to develop policies about transfer to tertiary centres and

implementation of Telehealth to ensure that all patients with pancreatic cancer receive optimal multidisciplinary coordinated care.

Chapter 5: Patterns of care

5.1. INTRODUCTION

This chapter includes a paper published in 2015. The aims of this publication were to describe the cohort included in the pancreatic cancer patterns-of-care study, to provide a broad overview of initial treatment patterns and to document overall survival.

5.2. CONTRIBUTION OF CANDIDATE

All authors contributed to the conceptualisation of the study. My contribution to this publication included data collection (20%). I completed the majority of the data cleaning (80%) with the help of MP and REN and all statistical analyses (100%). I was responsible for the interpretation of the results (32%) in consultation with the study team, in particular REN. I was also responsible for writing (70%), editing (35%) and submitting the manuscript (100%) taking into account the comments and suggestions of REN and the study team.

5.3. MANUSCRIPT

The following manuscript was published in the journal Pancreas:

Pancreas 2015; 44 (8):1259-65.

Describing Patterns of Care in Pancreatic Cancer – a population-based study

Burmeister EA, O'Connell DL, Beesley VL, Goldstein D, Gooden HM, Janda M, Jordan SJ, Merrett ND, Payne ME, Wyld D, Neale RE.

Authors have provided permission to include this publication in this thesis (Appendix I).

Abstract

Objectives: Despite pancreatic cancer being the 5th highest cause of cancer death in developed regions there is a paucity of population-based management details for patients with pancreatic cancer. The objective of this study was to reflect on current practice and outcomes to facilitate future improvement.

Methods: A comprehensive population-based patterns-of-care study in two Australian states was conducted. Patients diagnosed with pancreatic adenocarcinoma between July 2009 and June 2011 were identified by cancer registries, and detailed clinical data were collected from medical records.

Results: Data were collected for 1863 patients, 96% of those eligible. The majority resided in major cities, their median age was 72 years and 54% were men. Over half the cases (58%) had metastatic disease at diagnosis. Resection was attempted for 20% of patients but only completed in 15%. The

uptake of adjuvant chemotherapy (76%) and the proportion alive at one-year (22%) were higher than reported in previous population-based reports. Of those with no complete surgical resection, 43% received palliative chemotherapy.

Conclusion: This population-based overview of the management of patients with pancreatic cancer suggests that, despite evidence that the proportion surviving and the use of adjuvant chemotherapy has increased, there may still be under-utilisation of cancer-directed therapies.

Introduction

Pancreatic cancer is the 14th most common type of cancer diagnosed in the developed world.[1] It has a median survival of 6 months and an overall five-year survival of less than 5%. Consequently it is the 5th most common cause of cancer death in developed regions,[1] and current projections suggest that it will be the second leading cause of cancer death within 10 years.[40, 250]

Surgery offers the only possibility for cure, but the majority of patients present with metastatic or locally advanced disease which precludes curative resection. Co-morbidities and performance status in an older patient cohort may also influence the decision to withhold a radical surgical resection. Those patients who undergo an oncologically complete resection have five-year survival of approximately 15 to 20% compared with less than 5% for the 80% of patients who are inoperable.[271] Chemotherapy and radiotherapy are treatment options in neo-adjuvant, adjuvant or palliative settings, but these modalities offer minimal benefit in terms of survival.[99, 103, 272]

Best practice recommendations for management of pancreatic cancer were compiled by a group of experts at the World Congress on Gastrointestinal Cancer in 2006 (Barcelona 2006),[4] with additional recommendations for management of metastatic cancer made in 2012.[5] The United States National Comprehensive Cancer Network (NCCN) has also published clinical practice guidelines for pancreatic cancer.[6] Despite these publications it is apparent that there is considerable variation in the quality of management and care of patients with pancreatic cancer.[7-9]

There have been few attempts to describe management of pancreatic cancer at a population level, but evidence from the limited population-based studies that have been conducted in Australia (2011), Europe (2009) and the United States (2007) suggest that multimodality therapies are underutilised and that this may be related to patient and/or health-service characteristics.[12,13,15]

Data reflecting the current status of the variability in the management of patients with pancreatic cancer and the factors associated with the choice of different treatments is required. This will support changes in clinical practice and policy needed to optimise the care of all patients with this disease. We have therefore carried out a population-based study in two Australian states where over 50% of

Australians reside. In this report we describe the methods and patient cohort and provide a broad overview of care.

Materials and Methods

Patient identification and data from Cancer Registries

Eligible patients were those who were aged 18 years or older, notified to the Queensland (QLD) Cancer Registry between 1 July 2009 and 30 June 2011 or to the New South Wales (NSW) Cancer Registry (Cancer Institute NSW) between 1 July 2009 and 31st December 2010 with a diagnosis of pancreatic ductal adenocarcinoma (ICD-10 code C25).

From the cancer registries we obtained the patients' sex, age at diagnosis, date of initial diagnosis, name and address of the treating clinician at the time of the initial diagnosis, and the hospital where the diagnosis was made (if applicable). Where available we also obtained the date of death. The cancer registries also provided the statistical local area (SLA (QLD)) or local government area (LGA (NSW)) for the patients' residential locations. We used these to allocate patients to a level of socioeconomic status using the Socio-Economic Indexes for Areas (SEIFA) 2011[245] and geographical location based on the Accessibility/Remoteness Index of Australia (ARIA+) 2011.[246] The Index of Relative Socio-economic Disadvantage (IRSD) (SEIFA 2011) is a general index of disadvantage which uses data including income, home-ownership and occupation, captured in the five-yearly census, to rank areas in Australia according to relative socioeconomic advantage and disadvantage. We categorised patients according to their IRSD score by using the quintile cut-points for the state-specific population distributions. ARIA+ is derived from measures of road distances between populated localities and service centres. Areas are categorised as major cities, inner regional, outer regional, remote or very remote. Due to the small population in remote and very remote areas these were grouped with outer regional areas.

Ethical review:

We obtained approval to access medical records without patient consent under the QLD Public Health Act and under the guidelines of the NSW Privacy Act. Ethics approval was obtained from the QIMR Berghofer Medical Research Institute, the Royal Brisbane and Women's Hospital (on behalf of all public hospitals in QLD) and by the NSW Population and Health Services Research Ethics Committee. Additional ethics approvals and individual site-specific approvals were obtained for each public hospital and private hospital as required. All data collected for review was de-identified at source.

Clinical Data Collection:

Research nurses accessed medical records for each patient, commencing with the record from the facility where the diagnosis was made if possible. The nurses used a standardised case report form (CRF) to abstract very detailed data about patient management from the medical record. Discharge summaries and correspondence were checked for evidence of referral to other centres for further management, and medical records at these centres were also reviewed.

Information about initial presentation and investigations:

We captured information about initial symptoms, investigations and disease stage according to the International Union Against Cancer (UICC 6th Edition) tumour node metastasis classification system.[81] The tumour (T), node (N) and metastatic (M) status used to stage the disease was obtained from pathology reports on resection or, for those with no resection or missing TNM data, from initial investigations including imaging. We also classified patients according to the treating clinician's assessment of whether the tumour was resectable or not.

Initial Eastern Cooperative Oncology Group (ECOG) performance status and co-morbidities, such as cardiovascular disease, respiratory disease, renal impairment, diabetes and other cancers were noted and coded. Co-morbidity scores were then calculated using the Charlson index[244] and patients categorised into three groups according to their score: low (score equal to zero), medium (score equal to one) and high (score equal to two or more).

Information about treatment:

If patients underwent an attempted resection we recorded the place of surgery and the surgeon (both coded for anonymity), the surgical procedure performed (Whipple, total or distal pancreatectomy), surgical margins achieved and complications experienced. The reasons for not completing or attempting a resection were noted.

Information about other procedures such as insertion of biliary stents and bypass surgery was included along with any complications that arose as a result of these procedures. Nurses also extracted details for chemotherapy and radiotherapy including planned regimens, dates and doses of drugs/radiation administered, complications and responses. Symptom management was recorded, including prescription of replacement pancreatic enzymes, coeliac plexus blocks or use of opioids for pain management and treatment of nausea.

Dates of presentation at multidisciplinary team (MDT) meetings were noted as were referrals to social workers, physiotherapists, psychologists, palliative care services and dieticians. If the patient

had access to nursing care co-ordinators or had a documented care plan, these details were included on the CRF.

Information about admissions occurring until death or up to 12 months after the index admission were documented, including dates of admission and discharge, the types of health professionals involved in each episode of care, and all investigations and treatment.

At six and twelve months post diagnosis the patient's disease status and, if alive, place of residence was recorded. Date and cause of death was captured from the medical record if the patient died within 12 months of diagnosis. To update survival information we reviewed death information held by the Cancer Registries in February 2014.

Quality assurance:

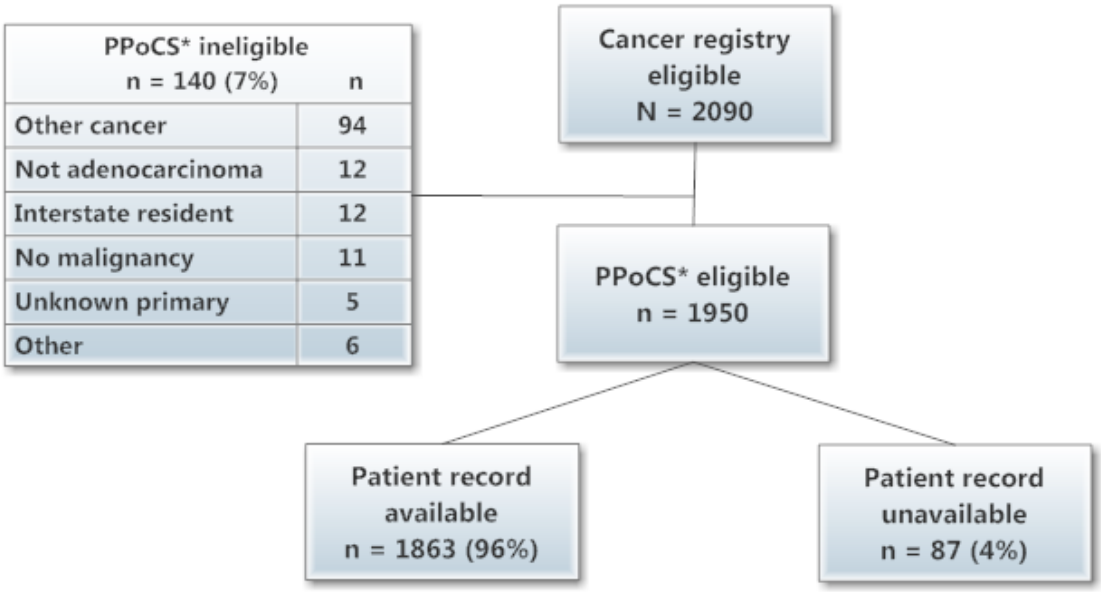
The research nurses who conducted the medical record reviews underwent an initial two-day training workshop with clinicians in attendance. This was repeated midway through the data collection period (after approximately 18 months). At these workshops all nurses reviewed the same series of charts and completed CRFs were compared. Discrepancies were discussed, and differences in interpretation resolved.

Statistical analysis

Descriptive statistics including frequencies and proportions were used to describe the cohort according to age, socio-economic status, place of residence, stage at diagnosis and patients' co-morbidities. Here we describe the overall treatment modalities as simple proportions, with cases with missing data omitted from denominators. Survival curves according to stage were generated applying Kaplan-Meier methods using the date of diagnosis until death of any cause, or February 20, 2014. Date of diagnosis was taken as the date of histological diagnosis or, for those with no histological diagnosis, the date of diagnosis via imaging.

Results

The NSW and QLD cancer registries identified 2090 patients as potentially eligible for inclusion in the cohort. Of these 140 (7%) were found to be ineligible after medical record review, most often because their cancer did not originate in the pancreas (n = 94, 67%). Charts were available for review for 1863 patients (96%); 87 reviews were not commenced due to difficulty accessing records or because the cancer registries were only notified when the patient died and no hospital information could be located. These have been excluded from all analyses (Figure 5-1).



*Pancreatic cancer patterns-of-care study

Notes: Other cancers included ampullary, cholangiocarcinoma, duodenal, gastric and other metastatic cancer; Interstate resident describes people diagnosed in QLD or NSW but who did not reside in these states; Other ineligibility includes diagnosed outside of study dates.

Figure 5-1: Flow chart of patient accrual and eligibility in QLD and NSW flow chart of patient accrual and eligibility in Queensland and New South Wales

Cohort and disease characteristics

The median age of those included in the cohort was 71 years (range 29 – 99) and 54% were men (Table 5-1). The sex distribution differed with age; 66% of patients 60 years or younger were male compared with 44% of those over 80 years. A SEIFA IRSD median score of 991 for the cohort showed that patients lived in slightly more disadvantaged areas than the Australian population (median 1000). The majority of patients (68%) lived in a major city at the time of diagnosis. Over half of the patients for whom we had information about co-morbidities (98% of all patients) had a Charlson co-morbidity index score of at least one.

Table 5-1: Sociodemographic and disease characteristics of pancreatic cancer patients in QLD and NSW (n=1863)

		n (%)[1]
Sex	Men	1015 (54)
Age at diagnosis, years	≤44	39 (2)
	45 - 54	137 (7)
	55 – 64	335 (18)
	65 - 74	552 (30)
	75 - 84	551 (30)
	≥ 85	249 (13)
Place of residence	Major cities	1257 (68)
	Inner regional	397 (22)
	Outer regional/remote /very remote *Unknown residence*	193 (10) 16 (1)
Socio-economic status – quintiles [2]	Most disadvantaged	372 (20)
	Second	399 (22)
	Third	383 (21)
	Fourth	390 (21)
	Least disadvantaged	303 (16)
	Unknown status	16 (1)
T Stage	T 0/1	44 (3)
	T 2	306 (20)
	T 3	876 (57)
	T 4	302 (20)
	Tumour cannot be evaluated (Tx)	335 (18)
N Stage	N0	338 (29)
	N1	827 (71)
	Regional lymph nodes cannot be evaluated (Nx)	698 (37)
M Stage	M0	782 (43)
	M1	1037 (57)
	Distant metastases cannot be evaluated (Mx)	44 (2)
TNM Stage	Stage I	85 (5)
	Stage II	507 (28)
	Stage III	148 (8)
	Stage IV	1036 (58)
	Undetermined stage	87 (5)
Confirmed tissue diagnosis		1368 (73)
Site	Head/neck/uncinate process	1184 (72)
	Body	156 (9)
	Tail	177 (11)
	Multiple/other	133 (8)
	Not stated	213 (11)
Potentially Resectable Disease	Yes	537 (30)
	No	1283 (70)
	Unknown	43 (2)
Charlson Comorbidity Index (score)	Low (0)	779 (43)
	Medium (1)	608 (33)
	High (≥2)	446 (24)
	Not stated	30 (2)
Performance Status	Fully active	447 (28)
	Limited activity	583 (36)
	In bed < 50% day	323 (20)
	In bed > 50% day	218 (14)
	Bed bound	29 (2)
	Not stated	263 (14)

Notes: 1: Undetermined or missing data are not included in the denominator for calculation of percentages.
2: Quintile cut-points are based on census data state population distributions.

Histological or cytological confirmation of disease was obtained in 73% of patients. The head, neck or uncinate process of the pancreas was affected in 72% of the cohort, and the body, tail or multiple sites were affected approximately equally for the remainder of those with known site. Almost a fifth of patients were missing tumour size (n = 335), and more than a third were missing nodal status (n = 698, 37%). However, because a large proportion of patients without this information had metastatic disease, the overall UICC stage was able to be derived for 95% of patients, 58% of whom were stage IV. Following investigations and staging 537 (30%) patients were thought to have potentially resectable disease but this varied according to the site of the tumour. Approximately 40% (449) of cancers in the head, neck or uncinate process were judged to be resectable compared with 12% (19), 21% (37), and 12% (16) in the body, tail or multiple sites respectively.

The median survival of the cohort was 4.5 months (95% confidence interval (CI) 1.7 to 10.8) with 22% alive one year after diagnosis (Figure 5-2).

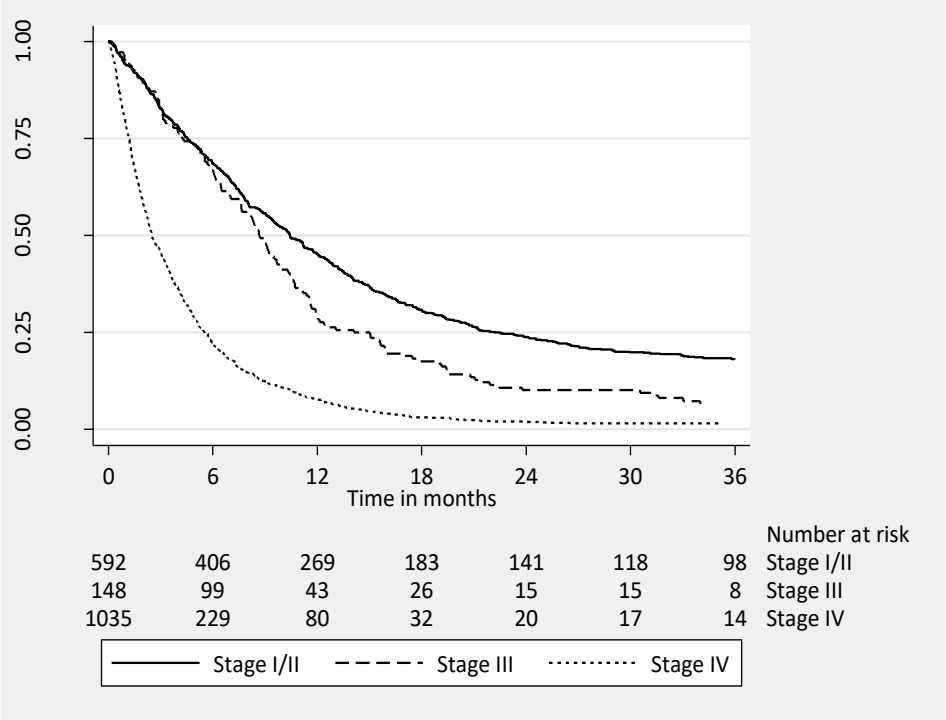


Figure 5-2: Survival for pancreatic cancer by stage at diagnosis in QLD and NSW

Median survival was 10.4 months (95% CI, 4.5 to 22.2) for patients diagnosed with stage I / II disease and 8.7 months (95% CI, 4.2 to 14.1) and 2.5 months (95% CI, 1.2 to 5.5) for those with stage III and stage IV disease, respectively.

Treatment

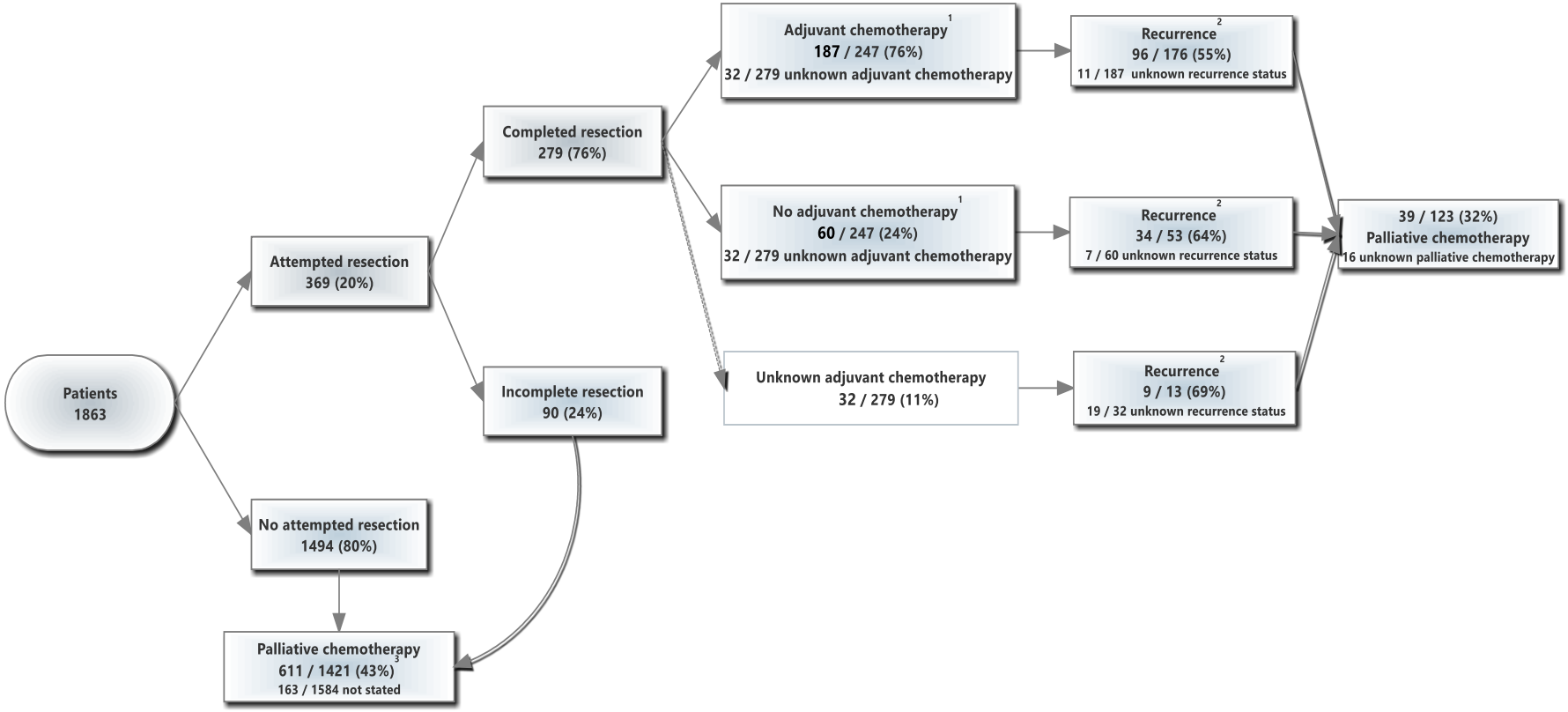
Figure 5-3 shows an overview of the management of this cohort. Resection was attempted for 369 patients (69% of those with potentially resectable disease, 20% of the total). Many patients (168, 31%) with potentially resectable disease did not undergo attempted curative surgery. The presence of co-morbidities accounted for the majority of these (n = 97; 58%). Advanced age was recorded as the primary reason for 31 patients (18%) and 34 (20%) declined surgery. The reason was unknown for 6 patients (4%). To enable comparison with other series, we also report the data for the 85 stage I patients. Fifty-eight percent (n = 49) did not undergo an attempted resection. For 30 patients (61%) the reason was old age and/or co-morbidities. Twelve patients (24%) declined surgery, and 4 (8%) had poor performance status. There were only 3 patients (6%) where no reason was recorded.

In approximately one quarter of patients who underwent an attempted resection it was not completed due to locally advanced disease (n = 50, 56%), the detection of metastases (n = 25, 28%), both local spread and metastases (n = 10, 11%) or unknown and other causes (n = 5, 6%). Only one stage I patient did not undergo a completed resection – this was due to the presence of liver cirrhosis. Ultimately 279 patients in this cohort (15%) had a completed curative surgical procedure.

Adjuvant chemotherapy was received by 187 (76%) of the 279 patients with completed surgical resections for whom we could find chemotherapy information (32 had missing data). Information about chemotherapy was missing for 163 (10%) of the 1584 patients who had an incomplete resection or no attempted resection. Where the information was recorded, palliative chemotherapy was given to 67% (n = 56) of those who had an attempted surgical resection, and 41% (n = 555) of those in whom surgery was not attempted (Figure 5-3).

Half of the patients (n = 139) who underwent a completed resection had recurrent disease within 12 months of diagnosis and 32% of these received palliative chemotherapy.

Radiotherapy was used infrequently. Only 151 patients (8%) underwent radiotherapy; 48 in an adjuvant and 103 in a palliative setting.



Notes: 1: Patients with unknown adjuvant chemotherapy information (n = 32) were removed from the denominator; 2: Recurrence within one year of diagnosis; 3: Including patients with incomplete resections.

Figure 5-3: Resection, recurrence and chemotherapy patterns of care for pancreatic cancer in QLD and NSW

Discussion

This is one of the most comprehensive studies of management of patients with pancreatic cancer conducted to date. We carefully reviewed medical records for a cohort of Australian patients with pancreatic cancer diagnosed over a two-year period. This broad overview of patient management has shown that, despite improvements in surgery and a relatively high number of people undergoing attempted resection, the number of patients having successful resections has only increased marginally compared to historical reports.[106, 273] Adjuvant treatment use, principally chemotherapy, is higher than in previous series,[12, 13, 18] which may explain the slightly higher survival than has been reported in other population-based cohorts.[12, 33]

The demographic characteristics of this cohort are consistent with other Australian and international data. The median age of 71 is identical to that reported in the United States SEER data[274] and the proportion who are male is as expected: 55% of patients included in our cohort compared with 53% of pancreatic cancer patients in the Australian cancer registry data in 2010[275]. With respect to geographical location, the distribution of our cohort is almost identical to that of the Australian population,[276] suggesting that the risk of pancreatic cancer does not differ appreciably according to remoteness. A slightly higher proportion of patients lived in more disadvantaged areas compared with the population distribution.[277]

Comparable to previous international reports,[273, 278] approximately 30% of patients were assessed as having potentially resectable disease. Of these, 30% did not progress to an attempted resection and, for those where resection was attempted, a large proportion was aborted (24%). This high number of incomplete resections may indicate incomplete or inadequate staging for patients with higher staged disease, or suggest that surgeons are more willing to attempt resections given improvements in surgical techniques that have occurred.[279] We observed that 58% of patients with stage I disease did not undergo attempted resection. This is lower than the 71% found in a series of patients diagnosed between 1995 and 2004 in the United States. However the proportion not resected in that cohort changed from 79% in 1995 to 64% in 2004 and it is possible that this has reduced further in the last decade.

Ultimately, 15% of all patients had a completed resection. This is marginally higher than previous Australian[107] European,[12] and United States[13, 33] reports of around 12%. It is possible that we have over-estimated the proportion who had resection due to failure to capture information about all patients, but if the 87 patients whose records we could not access were included in the dataset and assumed not to have undergone resection, the proportion resected would be 14%. This slightly

higher proportion may reflect surgical improvements enabling resection of tumours with a greater degree of vessel and nerve involvement than was previously possible,[265] but this nevertheless highlights the dismal prognosis for most patients diagnosed with pancreatic cancer. Identification of biomarkers that predict outcomes may lead to improvements in patient selection,[280] thereby avoiding surgical intervention in those where benefit will be marginal but possibly increasing the use of surgery in patients for whom benefit is not currently considered to outweigh risk.

Three quarters of patients who had a completed resection had adjuvant chemotherapy. In comparison, studies from the United States,[13] Australia[18] and Ireland,[12] all of which collected data for patients diagnosed over a decade ago, reported that the proportion of patients having adjuvant chemotherapy ranged from 39%[12] to 47%.[18] This may be due to increased use of adjuvant chemotherapy following the release of results from the ESPAC-1[157] and CONKO-001[3] trials and may be responsible for the somewhat higher survival than in earlier population-based studies (22% surviving to one year in our cohort compared with 15% or less previously).[12, 33]

Guidelines suggest that chemotherapy should be considered in the palliative care setting, dependent upon a patient's performance status,[5, 6, 190] as it has been shown to improve both survival[151] and quality of life.[281] Recent data identifying novel regimens that for the first time have shown incremental improvement over previous standards of care for chemotherapy mandate an understanding of contemporary practice in order to judge the impact of these new treatments over time.[282, 151] We observed that 43% of patients who did not undergo a completed resection received palliative chemotherapy. This is higher than some international population studies with rates of 20 to 30% [12, 62] but similar to previous Australian findings.[18] Under assumptions of all those with missing information either receiving or not receiving chemotherapy, the proportions would range from 32% to 54%, possibly indicating under-use of this treatment modality.

A major strength of this study is that it is truly population-based. Although we only included patients from two of the eight Australian states and territories, approximately 56% of all Australians live in these two states. The concordance of age, sex, stage and tumour site with reports from cancer registries and previous literature confirms that the cohort is essentially representative of the broader pancreatic cancer patient population and, while information for some items was difficult to obtain, we captured some data for 96% of all eligible patients diagnosed during the study period. The manual extraction from medical records by trained nurses was time- and labour-intensive, but it has resulted in much more detailed and complete data than would be possible through linkage.[283, 284] A previous Victorian population-based study collected data using

questionnaires sent to treating clinicians,[107] potentially leading to differences in the interpretation of data items. We carefully trained our staff to ensure reliable capture of information and regularly assessed data consistency across collectors.

In conclusion we have undertaken a comprehensive assessment of the patterns of care for patients diagnosed with pancreatic cancer in Australia. In this broad overview we show that there has been a small increase in the proportion of patients undergoing surgery and that the use of adjuvant chemotherapy in Australia appears to have increased somewhat in the last decade compared to previous Australian data from Victoria.[18, 107] Nevertheless, there remains under-utilisation of cancer-directed therapies which may contribute to the failure to improve outcomes in this difficult disease.

Chapter 6: Determinants of survival in pancreatic cancer patients with non-metastatic disease

6.1. INTRODUCTION

The work in this chapter was published in Pancreatology in 2016. The aim of this publication was to estimate the survival of patients with non-metastatic disease and factors associated with survival. As surgical resection of the tumour is the only potential strategy for increasing survival, factors associated with receipt of resection were also compared. As resection is only attempted in patients classified as having resectable disease, factors associated with this classification were also examined.

6.2. CONTRIBUTION OF CANDIDATE

My contribution to this publication included defining the relevant research question (70%) and data collection (20%) with the advice and support from REN and the study team. I completed the majority of the data cleaning (80%) and statistical analyses (80%), with the help of MW and REN, and I was responsible for the interpretation of the results (35%) in consultation with the study team, in particular REN. With input from REN and the study team I was also responsible for writing (70%), editing (32%) and submitting the manuscript (90%).

6.3. MANUSCRIPT

The following publication detailing these findings has been published in the journal Pancreatology:

Pancreatology 2016; 16 (5): 873-881.

Determinants of survival and attempted resection in patients with non-metastatic pancreatic cancer: an Australian population-based study.

EA Burmeister, M Waterhouse, SJ Jordan , DL O'Connell, ND Merrett, D Goldstein, D Wyld, V Beesley, H Gooden, M Janda, RE Neale

Authors have provided permission to include this publication in this thesis (Appendix I).

Abstract

Background

There are indications that pancreatic cancer survival may differ according to sociodemographic factors, such as residential location. This may be due to differential access to curative resection. Understanding factors associated with the decision to offer a resection might enable strategies to increase the proportion of patients undergoing potentially curative surgery.

Methods

Data were extracted from medical records and cancer registries for patients diagnosed with pancreatic cancer between July 2009 and June 2011, living in one of two Australian states. Among patients clinically staged with non-metastatic disease we examined factors associated with survival using Cox proportional hazards models. To investigate survival differences we examined determinants of : 1) attempted surgical resection overall; 2) whether patients with locally advanced disease were classified as having resectable disease; and 3) attempted resection among those considered resectable.

Results

Data were collected for 786 eligible patients. Disease was considered locally advanced for 561 (71%) patients, 510 (65%) were classified as having potentially resectable disease and 365 (72%) of these had an attempted resection. Along with age, comorbidities and tumour stage, increasing remoteness of residence was associated with poorer survival. Remoteness of residence and review by a hepatobiliary surgeon were factors influencing the decision to offer surgery.

Conclusions

This study indicated disparity in survival dependent on patients' residential location and access to a specialist hepatobiliary surgeon. Accurate clinical staging is a critical element in assessing surgical resectability and it is therefore crucial that all patients have access to specialised clinical services.

Introduction

Pancreatic cancer is the 10th most commonly diagnosed cancer in more developed regions of the world. However, it has the worst prognosis of any cancer, with a five-year relative survival of less than 5%, so is the 4th most common cause of cancer death.[1] Although survival rates have improved slightly over the past decade, current projections suggest that it will be the second leading cause of cancer death in the United States within 10 years.[40]

Worse survival has been observed for patients who live outside metropolitan areas,[285] have low socioeconomic status and who are elderly.[286] While patient factors such as frailty and comorbidities may be partially responsible for these survival differences, isolation and access to quality care may also play a role. This access to care is becoming increasingly important as vascular reconstruction becomes more commonplace in major centres, particularly in combination with neoadjuvent therapies for borderline resectable tumours. Multimodality therapy which includes complete surgical removal of the tumour currently provides the only potentially curative therapeutic

option,[265, 287, 288] improving five-year survival to about 20%.[113, 289, 290] However, due to the proximity of the pancreas to large vessels and organs, assessment of resectability is challenging and surgical resection itself is technically challenging.[102] National Cancer Comprehensive Network (NCCN) guidelines therefore recommend multidisciplinary consultation when determining potential resectability,[6] with the involvement of a skilled, specialised hepatobiliary surgeon as an integral part of the team.[291, 292] International data show that resection rates are influenced by ethnicity, insurance status, marital status, education level, socioeconomic status and geographical distance from large metropolitan areas.[10-13] There are indications that this may be related to the expertise at the facility where patients are being staged.[93]

Understanding factors that influence survival and that are associated with surgical resection may enable implementation of strategies to ensure all patients with pancreatic cancer who are suitable for surgery are indeed offered such potentially curative surgery as part of their management. Using data from an Australian population-based study of patients clinically staged as having non-metastatic pancreatic cancer, our aim was to investigate survival according to patient, tumour and health-service factors and to examine components associated with determination of resectability and whether or not resection was attempted.

Methods

Study population and data collection

Data collection and regulatory approvals for the study have been described previously.[293] Briefly, the study included patients aged ≥18 years who were notified to the Queensland Cancer Registry between 1 July 2009 and 30 June 2011 or to the New South Wales Cancer Registry between 1 July 2009 and 31 December 2010 with a diagnosis of pancreatic ductal adenocarcinoma. We obtained demographic and initial diagnosis information from the cancer registries; trained research nurses collected detailed clinical data from medical records. Date of death was obtained from medical records or cancer registries. As all patients with metastatic disease on initial clinical staging are unsuitable for curative resection, analyses were restricted to patients with no evidence of metastatic disease on clinical staging.

Outcomes

The main outcomes were one- and two-year mortality, defined as death of any cause within one and two years of diagnosis respectively, and survival time. Survival time was defined as the number of months from diagnosis until death or, for patients still alive, until date of last follow-up (February

2014). The date of diagnosis was taken as either the date of first diagnosis on imaging or histology/cytology, whichever came first.

To investigate survival differences, we examined factors associated with: (1) attempted surgical resection for all patients with non-metastatic disease; (2) whether patients with locally advanced disease were classified as having potentially resectable disease (restricted to this patient group as disease confined to the pancreas is automatically classified as resectable); and (3) attempted resection for those considered resectable. Whether or not a tumour was considered to be locally advanced or resectable was extracted from medical specialist or multidisciplinary team (MDT) meeting notes.

Factors of interest

Patient characteristics: The patient factors of interest included age at diagnosis, sex, Eastern Cooperative Oncology Group (ECOG) performance status and Charlson comorbidity index.[244] Based on area of residence at the time of diagnosis, each person was allocated a socio-economic index for areas (SEIFA)[245] score and Accessibility/Remoteness Index of Australia (ARIA)[246] category. For analysis we grouped the SEIFA score into quintiles and collapsed the ARIA into three groups: major city; inner regional; and outer regional/remote/very remote.

Tumour characteristics: Tumour factors included the site within the pancreas (head/neck/uncinate process, body, tail or multiple/other) and clinical stage of the tumour (confined to the pancreas or locally advanced disease). Locally advanced disease was defined as localised (non-metastatic) disease spread beyond the pancreas.

Health service characteristics: Health-service factors included the type of specialist first seen, the volume (according to the number of patient presentations in the study) of the facility where the patient was first treated as an inpatient, whether the patient was reviewed by a MDT and if they were assessed by a hepatobiliary surgeon. A hepatobiliary surgeon was defined as a surgeon who had undergone recognised specialised hepatobiliary surgery training and/or was recognised by their peers as an experienced hepatobiliary surgeon. Receipt of any chemotherapy was also included in the analysis of the mortality and survival outcomes. Associations between investigations performed to clinically stage the patient's tumour including computerised tomography (CT) (+/- pancreas protocol), endoscopic ultrasound (EUS), endoscopic retrograde cholangio-pancreatography (ERCP), magnetic resonance imaging (MRI) or cholangiopancreatography (MRCP), and laparoscopy, and each of resectability and attempted resection were evaluated.

Statistical analysis

Survival curves were generated and median survival was estimated using Kaplan-Meier methods, and the median time of follow-up was estimated using reverse Kaplan-Meier methods.[247] The associations between all patient, tumour and health-care factors and one- and two-year mortality were examined using logistic regression and the crude odds ratios (ORs) were estimated. Hazard ratios (HRs) for overall survival were estimated using Cox proportional hazards models. All patient and tumour factors were then included in multivariable models to estimate adjusted odds ratios (AORs) or hazard ratios (AHRs). Models examining health-service factors included all patient and tumour factors and the receipt of chemotherapy.

Associations between patient/tumour/health-service factors and each of (1) attempted resection; (2) whether or not the tumour was staged as potentially resectable for patients with locally advanced disease; and (3) whether or not a resection was attempted among those who were considered resectable were examined using multivariable logistic regression. To understand associations between place of residence, age and other patient and health-service factors, Chi-squared tests were used.

Hierarchical mixed effects models, with hospital as a random intercept, were used to adjust for the effects of clustering within hospitals when assessing associations between the outcomes of interest and hospital volume.

Statistical analyses were performed in Stata13 (Statacorp, Texas). All p-values are two-sided and we considered $p < 0.05$ as an indication of statistical significance.

Results

Patient characteristics and disease stage

Overall, 786 patients (44%) were clinically staged as having non-metastatic disease at diagnosis. The median age of these participants was 70 years (range 29 - 99) and 54% were men. The majority (69%) lived in major cities, 21% resided in inner regional areas and 10% in outer regional or remote locations. Disease was considered locally advanced for 561 (71%) patients. About two-thirds (n = 510; 65%) were classified as having potentially resectable disease after staging (225 with disease confined to the pancreas and 285 with locally advanced disease) and resection was attempted for almost three-quarters (n = 365; 72%) of these.

Mortality and survival

Median survival was 10 months and the proportions of patients who died within one and two years of diagnosis were 58% (n = 454) and 80% (n = 626) respectively.

Increasing age, comorbidities, low performance status, more advanced clinical stage of disease and tumours in the body of the pancreas were associated with higher mortality and poorer survival outcomes (Table 6-1: Associations between patient, tumour and health-service characteristics and 1- and 2-year mortality and survival for patients diagnosed with non-metastatic disease (n = 786)Table 6-1, Figure 6-1).

Table 6-1: Associations between patient, tumour and health-service characteristics and 1- and 2-year mortality and survival for patients diagnosed with non-metastatic disease (n = 786)

		1-year mortality[a]			2-year mortality[a]			Overall survival[b]		
Exposure variable	N[c]	% dead	Crude OR (95% CI)	Adjusted OR[d] (95% CI)	% dead	Crude OR (95% CI)	Adjusted OR[d] (95% CI)	Median (months)	Crude HR (95% CI)	Adjusted HR[d] (95% CI)
Patient / tumour factors										
Age at diagnosis, years										
< 60	141	38.3	1.00	1.00	66.7	1.00	1.00	13.9	1.00	1.00
60 - 69	218	48.2	1.50 (0.97, 2.30)	1.34 (0.84, 2.15)	76.2	1.60 (1.00, 2.56)	1.45 (0.86, 2.45)	13.0	1.20 (0.95, 1.52)	1.05 (0.83, 1.34)
70 - 79	223	65.8	2.72 (1.76, 4.20)	2.31 (1.44, 3.73)	79.8	1.98 (1.22, 3.19)	1.69 (0.98, 2.91)	8.4	1.57 (1.24, 1.98)	1.33 (1.04, 1.69)
≥ 80	204	76.0	5.10 (3.19, 8.13)	3.48 (2.05, 5.91)	92.2	5.88 (3.16, 10.91)	3.99 (1.94, 8.24)	5.0	2.70 (2.14, 3.42)	2.01 (1.56, 2.60)
Overall p-value, p-trend			<0.001, <0.001	<0.001, <0.001		<0.001, <0.001	0.003, <0.001		<0.001, <0.001	<0.001, <0.001
Sex										
Men	422	54.3	1.00	1.00	77.5	1.00	1.00	11.2	1.00	1.00
Women	364	61.8	1.36 (1.03, 1.81)	1.18 (0.85, 1.63)	82.1	1.34 (0.94, 1.90)	1.22 (0.81, 1.85)	8.8	1.25 (1.07, 1.45)	1.22 (1.04, 1.42)
Overall p-value			0.03	0.33		0.11	0.34		0.004	0.012
ECOG performance status										
Fully active	260	37.3	1.00	1.00	65.9	1.00	1.00	15.2	1.00	1.00
Not fully active	420	68.8	3.71 (2.68, 5.13)	2.53 (1.76, 3.64)	88.1	4.19 (2.84, 6.18)	2.90 (1.87, 4.51)	7.2	2.13 (1.79, 2.53)	1.74 (1.45, 2.08)
Overall p-value			< 0.0001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001
Charlson comorbidity index (score)										
Low (0)	340	49.1	1.00	1.00	74.1	1.00	1.00	12.4	1.00	1.00
Medium (1)	243	57.6	1.40 (1.01, 1.96)	1.12 (0.77, 1.63)	80.3	1.42 (0.95, 2.11)	1.10 (0.70, 1.73)	9.9	1.20 (1.00, 1.43)	1.04 (0.86, 1.25)
High (≥ 2)	199	72.9	2.78 (1.91, 4.06)	2.50 (1.64, 3.81)	88.9	2.81 (1.70, 4.66)	2.22 (1.26, 3.91)	8.0	1.62 (1.34, 1.95)	1.43 (1.18, 1.74)
Overall p-value, p-trend			<0.001,<0.001	<0.001, <0.001		<0.001,<0.001	0.02, 0.010		<0.001,<0.001	<0.001, 0.001
Place of residence										
Major city	547	56.5	1.00	1.00	77.9	1.00	1.00	10.4	1.00	1.00
Inner Regional	163	58.9	1.10 (0.77, 1.58)	1.19 (0.80, 1.79)	81.6	1.26 (0.81, 1.96)	1.54 (0.92, 2.59)	10.1	1.11 (0.93, 1.34)	1.17 (0.97, 1.42)
Outer regional/remote	76	64.5	1.40 (0.85, 2.31)	1.56 (0.88, 2.77)	88.2	2.11 (1.02, 4.36)	3.10 (1.34, 7.20)	8.4	1.29 (1.00, 1.66)	1.33 (1.03, 1.72)
Overall p-value, p-trend			0.40, 0.19	0.27, 0.11		0.096, 0.03	0.01, 0.003		0.11, 0.036	0.04, 0.01

Exposure variable	N[c]	1-year mortality[a]			2-year mortality[a]			Overall survival[b]		
		% dead	Crude OR (95% CI)	Adjusted OR[d] (95% CI)	% dead	Crude OR (95% CI)	Adjusted OR[d] (95% CI)	Median (months)	Crude HR (95% CI)	Adjusted HR[d] (95% CI)
Socio-economic Status of area of residence - quintiles										
Most disadvantaged	156	63.5	1.00	1.00	82.0	1.00	1.00	8.8	1.00	1.00
Second	171	57.3	0.77 (0.50, 1.21)	0.91 (0.55, 1.50)	77.8	0.77 (0.44, 1.32)	0.91 (0.49, 1.68)	10.1	0.87 (0.69, 1.10)	1.03 (0.81, 1.31)
Third	158	54.4	0.69 (0.44, 1.08)	0.68 (0.41, 1.14)	78.5	0.80 (0.46, 1.39)	0.81 (0.43, 1.52)	10.8	0.85 (0.67, 1.08)	0.81 (0.63, 1.04)
Fourth	160	56.9	0.76 (0.48, 1.19)	0.91 (0.54, 1.51)	78.1	0.78 (0.45, 1.36)	0.95 (0.51, 1.78)	10.3	0.90 (0.71, 1.14)	1.05 (0.83, 1.34)
Least disadvantaged	136	56.6	0.75 (0.47, 1.20)	0.80 (0.47, 1.35)	82.4	1.02 (0.56, 1.86)	1.05 (0.54, 2.05)	10.4	0.93 (0.73, 1.19)	1.01 (0.79, 1.31)
Overall p-value, p-trend			0.57, 0.26	0.64, 0.46		0.76, 0.97	0.94, 0.86		0.70, 0.71	0.22, 0.86
Tumour site										
Head/neck/uncinate process	647	58.4	1.00	1.00	81.1	1.00	1.00	10.1	1.00	1.00
Body	40	67.5	1.48 (0.75, 2.92)	1.71 (0.81, 3.62)	87.5	1.63 (0.62, 4.24)	1.92 (0.68, 5.42)	8.8	1.20 (0.87, 1.67)	1.40 (1.00, 1.96)
Tail	43	41.9	0.51 (0.27, 0.96)	0.63 (0.32, 1.24)	58.1	0.32 (0.17, 0.61)	0.36 (0.18, 0.72)	18.3	0.53 (0.36, 0.77)	0.60 (0.41, 0.88)
Multiple/other	33	51.5	0.76 (0.38, 1.52)	0.77 (0.35, 1.68)	81.8	1.05 (0.42, 2.59)	1.13 (0.41, 3.10)	11.7	0.93 (0.63, 1.35)	1.10 (0.75, 1.62)
Overall p-value			0.091	0.22		0.003	0.02		0.005	0.008
Clinical Stage										
Confined to pancreas	225	45.8	1.00	1.00	68.0	1.00	1.00	13.4	1.00	1.00
Locally advanced	561	62.6	1.98 (1.45, 2.71)	2.13 (1.48, 3.06)	84.3	2.53 (1.76, 3.63)	2.55 (1.68, 3.87)	9.3	1.59 (1.34, 1.89)	1.54 (1.29, 1.83)
Overall p-value			<0.001	<0.001		< 0.001	<0.001		<0.001	< 0.001
Health Service Factors										
Evidence of MDT review										
No/ Not stated	518	61.8	1.00	1.00[e]	81.9	1.00	1.00[e]	9.3	1.00	1.00[e]
Yes	268	50.0	0.62 (0.46, 0.83)	0.80 (0.56, 1.14)	75.4	0.68 (0.48, 0.97)	0.77 (0.50, 1.18)	11.9	0.76 (0.65, 0.89)	0.88 (0.74, 1.04)
Overall P value			0.002	0.22		0.033	0.22		0.001	0.14
First facility volume (number of patients)										
30 +	411	52.1	1.00	1.00[e]	76.2	1.00	1.00[e]	11.4	1.00	1.00[e]
10 - 29	232	60.3	1.40 (1.01, 1.94)	1.17 (0.79, 1.72)	81.0	1.34 (0.90, 1.99)	0.93 (0.58, 1.49)	9.3	1.20 (1.01, 1.43)	1.03 (0.86, 1.24)
< 10	132	74.2	2.65 (1.72, 4.10)	1.84 (1.07, 3.16)	90.2	2.87 (1.55, 5.31)	2.04 (0.91, 4.58)	7.2	1.71 (1.39, 2.09)	1.21 (0.95, 1.53)
Overall P value, P trend			0.043, <0.001	0.09, 0.04		0.003, 0.001	0.17, 0.23		<0.001, <0.001	0.29, 0.17
First specialist seen										
Hepatobiliary surgeon	145	50.3	1.00	1.00[e]	73.1	1.00	1.00[e]	12.0	1.00	1.00[e]
Gastroenterologist	235	54.5	1.18 (0.78, 1.79)	0.83 (0.51, 1.34)	78.7	1.36 (0.84, 2.20)	0.96 (0.55, 1.67)	11.2	1.23 (0.98, 1.55)	1.02 (0.80, 1.29)
General Surgeon	292	61.0	1.54 (1.03, 2.30)	0.87 (0.54, 1.40)	82.2	1.70 (1.06, 2.73)	1.04 (0.59, 1.82)	9.0	1.40 (1.13, 1.75)	0.99 (0.78, 1.26)
Other specialty	114	65.8	1.90 (1.14, 3.14)	0.90 (0.49, 1.65)	83.3	1.84 (1.00, 3.40)	0.91 (0.42, 1.94)	2.4	1.56 (1.20, 2.04)	0.92 (0.68, 1.23)
Overall P value			0.037	0.89		0.11	0.98		0.004	0.87

Exposure variable	N[c]	1-year mortality[a]			2-year mortality[a]			Overall survival[b]		
		% dead	Crude OR (95% CI)	Adjusted OR[d] (95% CI)	% dead	Crude OR (95% CI)	Adjusted OR[d] (95% CI)	Median (months)	Crude HR (95% CI)	Adjusted HR[d] (95% CI)
Seen by hepato-biliary surgeon										
No / Not stated	395	65.6	1.00	1.00[e]	87.1	1.00	1.00[e]	8.0	1.00	1.00[e]
Yes	391	49.9	0.52 (0.39, 0.70)	0.91 (0.64, 1.29)	72.1	0.38 (0.27, 0.55)	0.58 (0.37, 0.90)	12.1	0.61 (0.52, 0.70)	.81 (0.69, 0.96)
Overall P value			< 0.001	0.58		< 0.001	0.015		< 0.001	0.013
Received chemotherapy										
No / Not stated	387	74.4	1.00	1.00[e]	88.1	1.00	1.00[e]	5.5	1.00	1.00[e]
Yes	399	41.6	0.24 (0.18, 0.33)	0.34 (0.23, 0.50)	71.4	0.34 (0.23, 0.49)	0.50 (0.31, 0.82)	14.1	0.57 (0.48, 0.66)	0.58 (0.48, 0.70)
Overall P value			< 0.001	< 0.001		< 0.001	0.005		< 0.001	< 0.001
Resection										
No resection attempted	421	74.8	1.00	1.00[e]	92.4	1.00	1.00[e]	6.8	1.00	1.00[e]
Resection attempted	365	38.1	0.21 (0.15, 0.28)	0.39 (0.26, 0.57)	64.9	0.15 (0.10, 0.23)	0.30 (0.18, 0.52)	15.1	0.37 (0.32, 0.43)	0.56 (0.46, 0.68)
Overall P value			< 0.001	< 0.001		< 0.001	< 0.001		< 0.001	< 0.001

[a] Crude and adjusted odds ratios (ORs) estimated using logistic regression. P values are from Type 3 tests of effects using Wald's chi-square statistic. Overall P values are for test of association.

[b] Median survival estimated using Kaplan-Meier methods. Crude and adjusted hazards ratios (HRs) estimated using Cox proportional hazards (PH) and stratified Cox models, respectively. P values are from Type 3 tests of effects using Wald's chi-square statistic. Overall P values are for test of association.

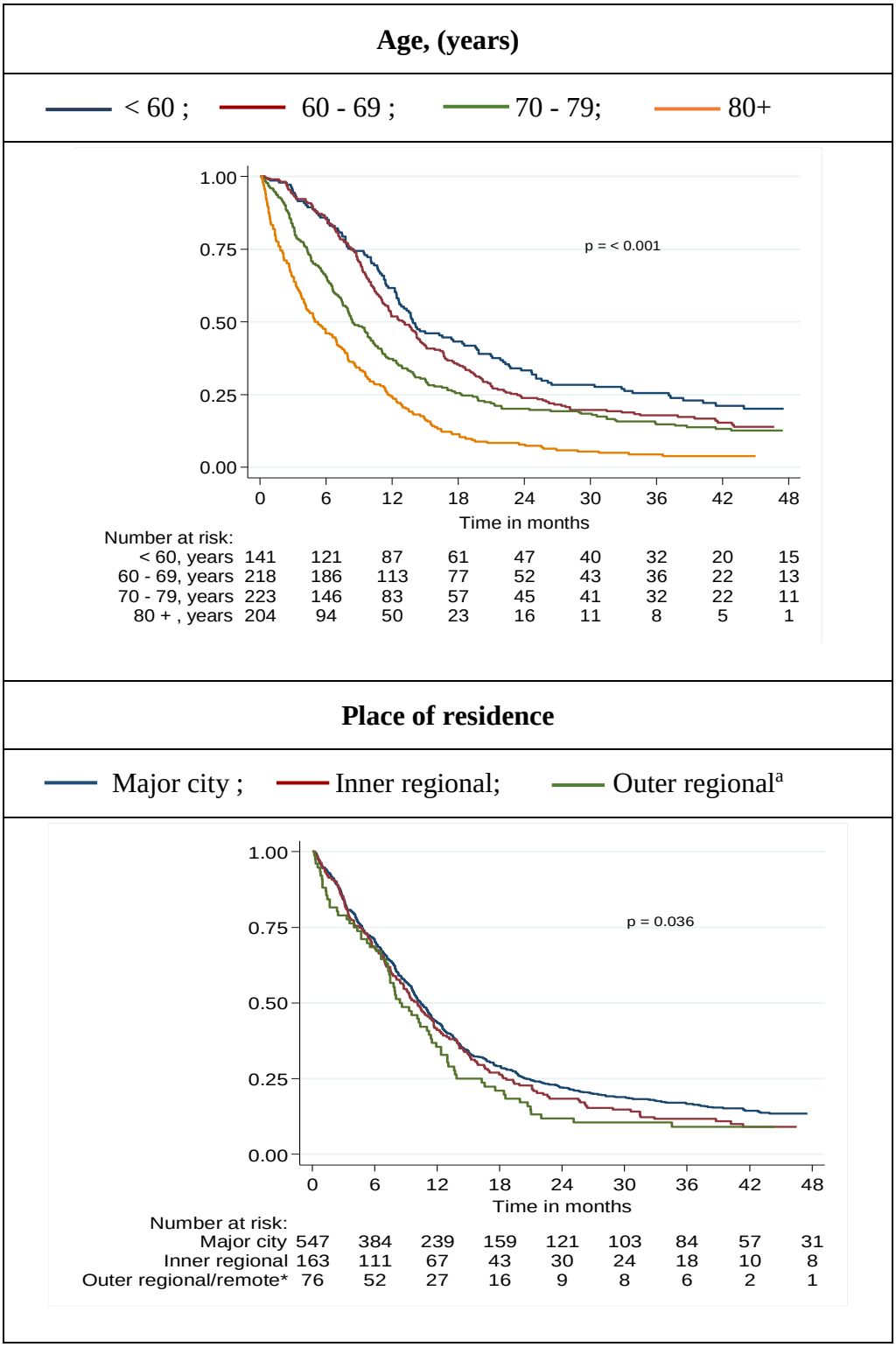
[c] Missing data: Socio-economic status, n= 5; Performance status, n = 106; comorbidities, n = 4; First facility volume , n = 11.

[d] Adjusted for patient (age, performance status (ECOG), place of residence(ARIA), Charlson comorbidity index) and tumour (clinical stage, site of tumour) factors. SES not adjusted for place of residence.

[e] Adjusted for patient and tumour factors and receipt of chemotherapy

Place of residence groups defined by Accessibility/Remoteness Index of Australia; ECOG, Eastern Cooperative Oncology Group; SES Socio-Economic Status defined by Socio-Economic Indexes for Areas; First facility volume by number of study participant initial presentations.

MDT: multidisciplinary team



P value calculated using log-rank tests to test the equality of survivor functions across age and place of residence groups.

[a] Outer regional includes remote and very remote regions

Figure 6-1: Kaplan-Meier survival curves by age at diagnosis and place of residence using the Accessibility/Remoteness Index of Australia (ARIA) for people diagnosed with non-metastatic pancreatic cancer (n = 786)

Compared with patients from major cities, risk of dying within two years was greater for patients from inner regional areas (AOR 1.54; 95% confidence interval [CI]: 0.92 - 2.59) and outer regional/ remote areas (AOR 3.10; 95% CI: 1.34 – 7.20). Increasing remoteness was associated with poorer survival (p trend = 0.01). Compared with those from major cities, those from outer regional/remote areas were 33% more likely to die (AHR 1.33, 95% CI: 1.03 – 1.72). This difference in survival remained after adjusting for attempted surgery (p trend = 0.01, AHR 1.31, 95% CI: 1.01 – 1.70). There were no associations between socio-economic status and mortality or survival in multivariable analyses. After adjusting for patient and tumour factors women had worse overall survival than men (AHR 1.22; 95% CI: 1.04 - 1.42), but when also adjusted for attempted surgery the difference was reduced and no longer statistically significant (AHR 1.15; 95% CI 0.99 – 1.35, p = 0.07).

Each health-service factor was associated with survival and mortality. Patients reviewed by an MDT had lower odds of dying up to one or two years after diagnosis and higher overall survival, but after adjustment for patient and tumour characteristics, the estimates were no longer statistically significant (Table 6-1). Being seen by a hepatobiliary surgeon was associated with improved overall survival (AHR 0.80; 95% CI: 0.69 – 0.96). Compared with patients who were first admitted to a facility that managed at least 30 pancreatic cancer patients annually, those first admitted to a hospital that treated fewer than 10 had higher one-year mortality (AOR 1.84; 95% CI: 1.07 – 3.16). Estimated survival and mortality rates were more favourable for patients who had an attempted resection (AHR 0.56; 95% CI: 0.46 - 0.68). Patients who received chemotherapy were less likely to die up to a year after diagnosis compared to those who had no record of chemotherapy treatment (AOR 0.34; 95% CI 0.23 – 0.50).

Determinants of attempted resection in all patients with non-metastatic disease

Older age, poorer performance status, and/or higher comorbidity scores were each significantly inversely associated with the likelihood of having resection attempted (Table 6-1 and supplementary Table 9-3). Patients from more remote areas had lower odds of attempted surgery compared with those living in major cities (AOR 0.61; 95% CI: 0.33 –1.10), although this was not statistically significant. Having tumour only in the tail of the pancreas was associated with a greater likelihood of attempted resection compared to having tumour in the head, neck or uncinate process (AOR 3.62; 95% CI: 1.58 – 0.33). Presentation at a MDT meeting and low volume of the facility where the patient was first admitted were associated with lower odds of having an attempted resection (AORs 0.60; 95% CI: 0.42 - 0.86, and 0.57; 95% CI: 0.34 - 0.97) respectively). If the

patient was seen by a hepatobiliary surgeon or had a staging laparoscopy they were more likely to have surgery (AORs 3.77; 95% CI: 2.63 – 5.39 and 4.84; 95% CI: 2.92 – 8.02 respectively).

Determinants of classification of cancer as resectable in patients with locally advanced disease

Factors associated with having a tumour classified as potentially resectable amongst patients with locally advanced disease were younger age (< 60 versus ≥ 70 years: 63% versus 44%, p < 0.01), better ECOG performance status (fully active versus not fully active: 59% versus 48%, p = 0.02) and living in a major city (remote vs major city/ outer regional: 53% versus 36%, p = 0.02) (Table 6-2). After adjustment for patient factors, the association with place of residence remained statistically significant (AOR 0.48; 95% CI: 0.26 –0.89) but further adjustment for health-service factors attenuated the association and it was no longer statistically significant (AOR 0.78; 95% CI: 0.38 – 1.59). Age remained associated with classification of resectability even after controlling for patient, tumour and health-service factors.

Patients presented at a MDT meeting were less likely to be assessed as having a potentially resectable tumour than those with no evidence of being reviewed by a MDT (AOR 0.33; 95% CI: 0.14 - 0.78). If patients were seen by a hepatobiliary surgeon they had almost twice the odds of being classified as having resectable disease (AOR 1.95; 95% CI 1.35- 2.82). Patients who underwent an EUS compared with those who did not were less likely to be classified as having potentially resectable disease (AOR 0.60; 95% CI: 0.41 – 0.86), whereas the opposite was observed if they had a laparoscopy (AOR 4.70; 95% CI: 2.77 – 7.98).

Determinants of attempted surgery in patients classified as having potentially resectable disease

Amongst those patients classified as potentially resectable we found that 28% (n = 145) did not proceed to surgery. The recorded reasons were predominantly comorbidities and/or age (88%, n = 127) with only 12% (n = 18) recorded as other or not stated. There were statistically significant associations between age, performance status and co-morbidities and whether surgery was attempted (Table 6-2). Patients from more remote areas had lower odds of attempted surgery compared with those living in major cities (AOR 0.61; 95% CI: 0.33 –1.10), although this was not statistically significant. Having tumour only in the tail of the pancreas was associated with a greater likelihood of attempted resection compared to having tumour in the head, neck or uncinate process (AOR 3.62; 95% CI: 1.58 – 0.33). Presentation at a MDT meeting and low volume of the facility where the patient was first admitted were associated with lower odds of having an attempted resection (AORs 0.60; 95% CI: 0.42 - 0.86, and 0.57; 95% CI: 0.34 - 0.97) respectively). If the

patient was seen by a hepatobiliary surgeon or had a staging laparoscopy they were more likely to have surgery (AORs 3.77; 95% CI: 2.63 – 5.39 and 4.84; 95% CI: 2.92 – 8.02 respectively).

Table 6-2: Associations between adjusted patient, tumour and health-service factors and (1) attempted resection (n = 786) ; (2) classification of disease resectability (n = 561); and (3) attempted resection for patients classified as resectable (n=510)

	(1) All Non-metastatic disease			(2) Locally advanced disease[a]			(3) Classified as resectable		
		Attempted resection			Classified as resectable			Attempted resection	
Variable	Total	N (%)	Adjusted OR[b] (95% CI)	Total	N (%)	Adjusted OR[b] (95% CI)	Total	N (%)	Adjusted OR[b] (95% CI)
PATIENT / TUMOUR FACTORS									
Age at diagnosis, years									
< 60	141	103 (73)	1[c]	98	62 (63)	1[c]	105	103 (98)	1[c]
60 - 69	218	135 (62)	0.59 (0.37, 0.94)	163	91 (56)	0.71 (0.42, 1.20)	146	135 (92)	0.22 (0.05, 1.04)
70 - 79	223	107 (48)	0.33 (0.21, 0.53)	161	76 (47)	0.51 (0.30, 0.85)	138	107 (78)	0.06 (0.01, 0.27)
≥ 80	204	20 (10)	0.04 (0.02, 0.07)	139	56 (40)	0.38 (0.22. 0.66)	121	20 (17)	0.00 (0.00, 0.02)
Overall p value, p trend			< 0.001, < 0.001			0.002, < 0.001			< 0.001, < 0.001
Sex									
Men	422	222 (53)	1[d]	299	164 (55)	1[d]	287	222 (77)	1[d]
Women	364	143 (39)	0.77 (0.55, 1.08)	262	121 (46)	0.74 (0.52, 1.05)	223	143 (64)	0.89 (0.48, 1.65)
Overall p value			0.13			0.09			0.71
Performance status									
Fully active	260	183 (70)	1[e]	160	95 (59)	1[e]	195	183 (94)	1[e]
Not fully active	420	134 (32)	0.24 (0.17, 0.35)	325	156 (48)	0.71 (0.47, 1.05)	251	134 (53)	0.06 (0.02, 0.14)
Overall p value			< 0.001			0.09			< 0.001
Charlson comorbidity index (score)									
Low (0)	340	184 (54)	1[e]	252	126 (50)	1[e]	214	184 (86)	1[e]
Medium (1)	243	105 (43)	0.78 (0.54, 1.14)	177	91 (51)	1.15 (0.78, 1.71)	157	105 (67)	0.40 (0.20, 0.80)
High (≥ 2)	199	74 (37)	0.59 (0.39, 0.88)	130	66 (51)	1.10 (0.72, 1.70)	135	74 (55)	0.15 (0.07, 0.31)
Overall p value, p trend			0.03, 0.01			0.76, 0.59			< 0.001, < 0.001
Place of residence									
Major city	542	258 (48)	1[d]	386	206 (53)	1[d]	362	258 (71)	1[d]
Inner Regional	163	74 (45)	0.84 (0.55, 1.28)	119	50 (50)	0.90 (0.59, 1.38)	104	74 (71)	0.68 (0.32, 1.46)
Outer regional / remote	76	31 (41)	0.61 (0.33, 1.10)	53	19 (36)	0.48 (0.26, 0.89)	42	31 (74)	0.44 (0.13, 1.50)
Overall p value, p trend			0.22, 0.09			0.07, 0.04			0.31, 0.13
Socio-economic status - quintiles									
Most disadvantaged	156	73 (47)	1[d]	110	55 (50)	1[d]	101	73 (72)	1[d]
Second	171	80 (48)	0.77 (0.46, 1.31)	123	65 (53)	1.01 (0.60, 1.72)	113	80 (71)	0.51 (0.19, 1.32)
Third	158	68 (43)	0.78 (0.46, 1.34)	113	50 (44)	0.72 (0.42, 1.24)	95	68 (72)	0.95 (0.34, 2.65)
Fourth	160	77 (48)	0.85 (0.50, 1.45)	107	56 (52)	0.95 (0.55, 1.65)	109	77 (71)	0.56 (0.21, 1.50)
Least disadvantaged	136	65 (48)	0.93 (0.53, 1.64)	105	59 (56)	1.19 (0.68, 2.07)	90	65 (72)	1.56 (0.55, 4.46)
Overall p value, p trend			0.86, 1.00			0.50, 0.69			0.18, 0.43

	(1) All Non-metastatic disease			(2) Locally advanced disease[a]			(3) Classified as resectable		
		Attempted resection			Classified as resectable			Attempted resection	
Variable	Total	N (%)	Adjusted OR[b] (95% CI)	Total	N (%)	Adjusted OR[b] (95% CI)	Total	N (%)	Adjusted OR[b] (95% CI)
Tumour site									
Head/neck/uncinate process	647	298 (46)	1[d]	463	240 (52)	1[d]	424	298 (70)	1[d]
Body	40	14 (35)	0.46 (0.21, 0.99)	29	8 (28)	0.33 (0.14, 0.77)	19	14 (74)	0.98 (0.19, 4.99)
Tail	43	33 (77)	3.62 (1.58, 8.33)	27	21 (78)	3.09 (1.20, 7.94)	37	32 (89)	3.39 (0.85, 13.57)
Multiple/other	33	13 (39)	0.55 (0.24, 1.24)	25	8 (32)	0.45 (0.18, 1.10)	16	13 (81)	1.25 (0.19, 8.13)
Overall p value			0.001			0.001			0.39
HEALTH SERVICE FACTORS									
Evidence of MDT review									
No / not stated	518	239 (46)	1[f]	355	193 (54)	1[f]	356	239 (67)	1[f]
Yes	268	126 (47)	0.60 (0.42, 0.86)	206	92 (45)	0.33 (0.14, 0.78)	154	126 (82)	1.09 (0.54, 2.21)
Overall p value			0.01			0.01			0.81
First facility volume[g]									
30 +	411	226 (55)	1[f]	275	153 (56)	1[f]	289	226 (78)	1[f]
10 – 29	232	97 (42)	0.70 (0.47, 1.05)	170	84 (49)	0.92 (0.61, 1.38)	146	97 (66)	0.52 (0.20, 1.537)
< 10	132	42 (32)	0.57 (0.34, 0.97)	107	48 (45)	0.88 (0.53, 1.45)	73	42 (58)	0.51 (0.15, 1.67)
Overall p value, p trend			0.06, 0.02			0.85, 0.58			0.34, 0.19
Specialist first seen									
Hepatobiliary surgeon	235	87 (60)	1[f]	87	44 (51)	1[f]	102	87 (85)	1[f]
Gastroenterologist	235	123 (52)	0.99 (0.61, 1.61)	173	97 (56)	1.42 (0.83, 2.43)	159	123 (66)	0.75 (0.29, 1.94)
General Surgeon	292	118 (40)	0.70 (0.43, 1.13)	222	108 (49)	1.11 (0.66, 1.89)	178	118 (66)	0.64 (0.25, 1.63)
Other	114	37 (32)	0.67 (0.36, 1.25)	79	36 (46)	1.08 (0.56, 2.08)	71	37 (52)	0.58 (0.19, 1.79)
Overall p value			0.24			0.52			0.77
Seen by hepato-biliary surgeon									
No / not stated	395	106 (27)	1[f]	308	129 (42)	1[f]	216	106 (49)	1[f]
Yes	391	259 (66)	3.77 (2.63, 5.39)	253	156 (62)	1.95 (1.35, 2.82)	294	259 (88)	6.78 (3.38, 13.59)
Overall p value			< 0.001			< 0.001			< 0.001
Pancreas protocol computerised tomography									
No / not stated	406	173 (43)	1[f]	294	150 (51)	1[f]	262	173 (66)	1[f]
Yes	380	192 (51)	0.96 (0.68, 1.35)	267	135 (51)	0.97 (0.61, 1.23)	248	192 (77)	1.33 (0.71, 2.50)
Overall p value			0.82			0.42			0.37
Plain computerised tomography									
No / not stated	261	133 (51)	1[f]	189	104 (55)	1[f]	176	133 (76)	1[f]
Yes	525	232 (44)	0.76 (0.54, 1.12)	372	181 (49)	0.79 (0.55, 1.15)	334	232 (69)	0.40 (0.19, 0.83)
Overall p value			0.17			0.22			0.01

	(1) All Non-metastatic disease			(2) Locally advanced disease[a]			(3) Classified as resectable		
		Attempted resection			Classified as resectable			Attempted resection	
Variable	Total	N (%)	Adjusted OR[b] (95% CI)	Total	N (%)	Adjusted OR[b] (95% CI)	Total	N (%)	Adjusted OR[b] (95% CI)
Endoscopic ultrasound									
No / not stated	434	186 (43)	1[f]	311	168 (54)	1[f]	291	186 (64)	1[f]
Yes	352	179 (51)	0.85 (0.60, 1.20)	250	117 (47)	0.60 (0.41, 0.86)	219	179 (82)	1.12 (0.59, 2.10)
Overall p value			0.35			0.006			0.74
Laparoscopy									
No / not stated	648	252 (39)	1[f]	455	201 (44)	1[f]	394	252 (64)	1[f]
Yes	138	113 (82)	4.84 (2.92, 8.02)	106	84 (79)	4.70 (2.77, 7.98)	116	113 (97)	12.15 (3.40, 43.40)
Overall p value			< 0.001			< 0.001			< 0.001
Endoscopic retrograde cholangiopancreatography									
No / not stated	399	190 (48)	1[f]	276	134 (49)	1[f]	257	190 (74)	1[f]
Yes	387	175 (45)	1.04 (0.74, 1.47)	285	151 (53)	1.26 (0.89, 1.79)	253	175 (69)	0.86 (0.46, 1.63)
Overall p value			0.81			0.20			0.65
Magnetic resonance imaging /cholangiopancreatography									
No / not stated	642	285 (44)	1[f]	462	236 (51)	1[f]	416	285 (69)	1[f]
Yes	144	80 (56)	1.10 (0.72, 1.68)	99	49 (49)	0.81 (0.51, 1.27)	94	80 (85)	1.42 (0.60, 3.35)
Overall p value			0.67			0.36			0.43

[a] Based on clinical staging including imaging or exploratory laparoscopy. [b] Crude and adjusted odds ratios (ORs,) calculated using logistic regression.

Adjustment variables: [c] Place of residence (major city, inner regional, outer regional/remote/very remote); [d] Age at diagnosis (<60, 60-69, 70-79, 80+ years) and performance status (0, 1, 2+, not stated); [e] Age at diagnosis; [f] Age at diagnosis, performance status and place of residence.

[g] Results from a mixed effects model with hospital as random intercept to adjust for hospital clustering.

Place of residence groups defined by Accessibility/Remoteness Index of Australia (ARIA); Performance status defined by Eastern Cooperative Oncology Group (ECOG); SES Socio-Economic Status defined by Socio-Economic Indexes for Areas; First facility volume by the number of study participant initial presentations.

Missing data: SES, n = 5; Place of residence, n = 5; Tumour site, n = 23; ECOG, n = 106; Charlson comorbidity index, n = 4; First inpatient facility volume, n = 11.

There was no difference in the proportion of patients who proceeded to attempted resection according to location of residence. After adjustment for age and performance status people living in more remote regions had non-significant lower odds compared to patients living in major cities. Most health system factors and investigations were significantly associated with attempted resection, but after adjusting for patient factors, only being seen by a hepatobiliary surgeon (AOR 6.78; 95% CI: 3.38 – 13.59) and having a laparoscopy (AOR 12.15; 95% CI: 3.40 – 43.40) were positively associated with attempted resection.

Associations between age, location of residence and health system factors

Age and place of residence were not significantly associated with each other, but both were associated with being assessed by a hepatobiliary surgeon, the specialist first seen and the facility volume where the patient was first an inpatient (Appendix E – Table 9-4). Patients living in more remote regions were less likely to undergo EUS and ERCP than those living in major cities, and older patients were less likely to undergo pancreas-protocol CT and MRI or MRCP, EUS or have laparoscopies as part of their clinical staging investigations. The likelihood of laparoscopy (8% versus 22%, p = 0.001) and EUS (33% versus 53%, p<0.001) was also lower for patients initially admitted to a low rather than high volume facility.

Discussion

In this population-based cohort of patients with non-metastatic pancreatic cancer we found, as expected, that those with more advanced disease and those who were older, who had poorer performance status or more co-morbidities were more likely to die within one or two years and had poorer overall survival. Lower survival was observed for people who lived in regional or remote areas compared with those living in capital cities, even after adjusting for differences in patient and tumour factors.

The percentage of patients with non-metastatic disease alive at one year (42%) in our cohort was considerably higher than the ~30% reported in some previous population-based studies[12, 33, 107] but similar to estimates from studies using more recent registry data.[60, 294] Our findings that clinical disease stage, performance status, presence of co-morbidities and age influence survival are consistent with international and national reports.[285, 286, 289, 295]

The proportion of our cohort classified as having potentially resectable disease was higher than that in previous international studies (65% versus 37% - 45%)[10, 294] with some studies suggesting that age, sex, medical insurance and site of the tumour are associated with resectability.[10, 195] Almost

three-quarters of those identified as resectable proceeded to an attempted resection which is considerably higher than the ~20-60% in earlier reports.[10, 12, 106, 294] The higher likelihood of being classified as having resectable disease and higher rates of attempted resection in this study may be due to temporal changes in the definition of resectability as surgical techniques have improved.[296]

The association between place of residence and survival has been observed in other settings[285] with travelling distance to receive treatment[297] and the lack of high-volume specialist centres in more rural areas[142] being suggested as reasons for this. Our results suggest that the poorer survival of patients living in regional and remote areas may be at least partially due to them being less likely to be classified as having resectable disease. Although they are equally likely to undergo surgery once classified as resectable, this results in a lower overall proportion undergoing surgery. While patients living in lower socio-economic areas or more distant from health services may choose not to undergo treatment, it is important that adequate staging to determine resectability is undertaken in order that they can make an informed decision about their treatment pathways.

We found that only half of the patients were reviewed by a hepatobiliary surgeon at any time during their disease course, and the proportion was significantly higher in metropolitan areas than in regional and remote areas and in younger than in older patients. Similarly, older patients and those living in remote areas were less likely to be first admitted to a high volume hospital. These results are inconsistent with guidelines[6, 94, 291] and the views of clinical experts[298] which recommend that all patients diagnosed with non-metastatic disease should be reviewed by an experienced hepatobiliary surgeon, ideally supported by a multidisciplinary team. A recent study reported that patients with non-metastatic pancreatic cancer had a greater likelihood of having surgical treatment when clinical staging was established in a specialised pancreatic cancer centre.[122] EUS is used to assess the tumour, vascular invasion, tissue diagnosis, lymph node disease, small volume liver disease and peritoneal ascites, all of which help to ascertain the resectability of the tumour. This may explain why patients who had this investigation were less likely to be classified as resectable. Laparoscopy, which is used selectively in most specialised units, tends to be used in patients thought to be resectable to detect potential small-volume peritoneal disease, so patients were more likely to proceed to surgery following this investigation. We also demonstrated that being seen by a hepatobiliary surgeon was associated with a greater likelihood of being diagnosed with resectable disease. While this may be due to reverse causality, being seen by a hepatobiliary surgeon appears to mediate the association between location of residence and classification of tumour resectability, suggesting that improving access to specialist care may increase the proportion of patients living in non-metropolitan areas who undergo surgery.

Review by a MDT is the standard of care for patients without metastatic disease[6] and has been shown to improve survival.[170, 299] We found that review by an MDT was associated with a lower likelihood of being classified as having resectable disease, most likely because clinicians tended to present patients with borderline resectable disease to the MDT. Despite this, after adjustment for patient factors, MDT review was associated with improved overall survival, both for patients who did and did not undergo surgery (Appendix E: Table 9-5), suggesting that MDT management is an indicator of improved overall care. A follow-up study focussed specifically on multidisciplinary care is needed to determine which patients are presented to MDTs and to understand the consequences of not being presented to a specialist MDT in a high-volume hospital.

Given the challenges of pancreatic cancer surgery and its subsequent survival even after potentially curative resection, it is appropriate that consideration of quality of life and other patient factors influence the decision to proceed to recommending resection. In keeping with this, we found that age, poor performance status or the presence of co-morbidities were given as the reason for surgery not to proceed in patients with potentially resectable disease. Our results may, however, indicate that in some cases older patients may be considered to have non-resectable disease by default and without adequate staging or review by an expert team. In the absence of poor performance status or significant comorbidities age is not necessarily a contraindication to surgery[220] and may indicate a nihilistic attitude amongst some clinicians.[300] This emphasises the importance of a full staging work up so that patients can make informed decisions about their treatment, irrespective of their age.

Major strengths of our study include the large population-based sample and the comprehensive data collected. However, our classification of clinical disease stage as confined to the pancreas, locally advanced or metastatic disease, did not allow for the separate classification of borderline resectable disease. Pancreatic cancers are categorised on a continuum from resectable to unresectable according to involvement of adjacent structures and the presence of distant metastases[296, 301] but this categorization was performed by numerous surgeons in this study and may not be consistent. International more robust criteria for defining resectable disease were introduced after the study period.[6, 105] It is also possible that at least some of the associations with hospital volume, laparaoscopy and hepatobiliary surgeon review arose due to reverse-causality.

In conclusion this study found disparities in survival dependent on where patients live and where and by whom they are managed. Initial accurate clinical staging is a critical element in the provision of optimal management, with access to hepatobiliary surgeons, high volume specialist facilities and multidisciplinary teams shown to be important. Many patients do not meet the

guidelines that recommend an early review by a hepatobiliary surgeon and by a MDT, with access to these services partly dependent on where patients live. Designing health services and referral patterns that ensure all patients receive appropriate staging and expert assessment, regardless of where and how they enter the health system, has the potential to lead to improvements in survival.

Chapter 7: Quality-of-care score

7.1. INTRODUCTION

This chapter includes a paper published in the Medical Journal of Australia. The aims of this publication were to:

1. Investigate factors associated with the quality-of-care score for patients with pancreatic cancer and
2. Examine the association between the quality-of-care score and overall survival

7.2. CONTRIBUTION OF CANDIDATE

My contribution to this publication included conceptualising the research question (70%) with significant input from REN and support from DO and the study team. I completed all data collection to develop the score and 20% of the patterns-of-care study data. I also completed the majority of the data cleaning (90%) and statistical analyses (70%) with the help of REN and DO. I was responsible for the interpretation of the results (40%) in consultation with the study team and in particular REN. I wrote (55%), edited (34%) and submitted the manuscript (90%) with REN providing significant writing and editing assistance and with valuable contributions from the study team.

7.3. MANUSCRIPT

The following manuscript has been published by the Medical Journal of Australia:

MJA 2016; 10 (25): 459-465.

Factors associated with quality of care in patients with pancreatic cancer.

Burmeister EA, O'Connell DL, Jordan SJ, Goldstein D, Merrett ND, Wyld D, Beesley VL, Gooden HG, Janda M, Neale RE.

Authors have provided permission to include this publication in this thesis (Appendix I).

Abstract

Introduction

Caring for patients with pancreatic cancer is challenging and there is evidence that the quality of care differs according to sociodemographic factors. Our aim was to develop a composite quality-of-care score, to examine variation in care by patient and health-service factors and to assess whether the score is associated with survival of Australian patients with pancreatic cancer.

Methods

Patients diagnosed with pancreatic cancer between July 2009 and July 2011 in Queensland and New South Wales were allocated a quality-of-care score based on a list of care items derived using a Delphi process. The score ranged from 0 to 1, with a higher score indicating better quality care. Associations between patient and health-service factors and the score were tested using linear regression. We examined associations with survival using Kaplan-Meier and Cox proportional hazards methods.

Results

Scores were assigned to 1571 patients. Significantly higher scores were observed for patients living in major cities versus more rural areas (adjusted difference: 0.11), in least versus most disadvantaged areas (adjusted difference: 0.08), who were younger, had better performance status and who first presented to a highvolume centre. Higher scores were associated with improved survival; after adjusting for patient factors each 10% absolute increase in the score reduced the risk of dying by 6% (hazard ratio 0.94; 95% CI 0.91-0.97).

Conclusion

This study provides evidence that place of residence influences the quality of care received and that survival outcomes may improve for patients with pancreatic cancer if they receive optimal management.

- The known: Treating patients with pancreatic cancer is challenging and sociodemographic factors can influence receipt of treatment modalities such as surgery and chemotherapy.
- The new: We developed a composite quality-of-care score and found that it was lower for patients who lived in rural or socially disadvantaged areas. It was higher for patients who first presented to a high volume hospital. The score was significantly associated with survival.
- The implications: Strategies need to be developed to ensure that all patients with pancreatic cancer have the opportunity to receive optimal care delivered by or in conjunction with high volume expert centres.

Introduction

In Australia, pancreatic cancer is the 10th most common cancer and the 4th leading cause of cancer-related death.[35] One-year overall survival is 20%; five-year survival is 6%.[36] Pancreatic cancer presents distinct management challenges, requiring highly specialised care.

A systematic review has shown that optimal care increases the likelihood of desired health outcomes in pancreatic cancer.[251] Studies from Australia and internationally have shown that fewer patients receive recommended treatment than expected,[12, 293] receipt of recommended care is inconsistent,[10, 119] and that sociodemographic factors influence management.[10, 220] Treatment in non-specialised centres appears to be at least partly responsible for these associations.[93, 302]

Previous studies have tended to focus on individual management modalities, such as surgery or chemotherapy. We took a more holistic approach and calculated an overall quality-of-care score for Australian patients diagnosed with pancreatic cancer. We examined variation in the score by patient and health-service factors and analysed the association between the quality of care delivered and survival.

Methods

This analysis was nested within a population-based study of patterns of care in Australian patients with pancreatic cancer. Eligible patients were residents of Queensland and New South Wales diagnosed with pancreatic cancer between July 2009 and June 2011. Trained research nurses collected information about patient management from medical records in public and private facilities.[293] We excluded patients who died within a month of diagnosis or had clinical staging data unavailable from this care score analysis.

We calculated a quality-of-care score based on results of our previously reported Delphi process.[298] Briefly, clinicians from a range of specialties involved in pancreatic cancer care were asked "What is important in the care of patients with pancreatic cancer". Thematic analysis of the responses resulted in a list of statements. The clinicians were asked to score each statement ranging from 0 (disagree, not important) to 10 (strongly agree, very important). The mean and coefficient of variation (CV) were determined for each statement.

Calculating the quality-of-care score

We used the mean scores from the Delphi process to calculate a quality-of-care score, selecting statements where there was reasonable consensus from the Delphi participants (CV $\leq$ 0.4) and

where information to assess whether or not the item of care had been delivered was available in our database. Eighteen items were included (Table 7-1).

For each patient we calculated a potential score by identifying the items which applied to their clinical situation and summing the mean scores obtained from the Delphi survey for these items. For example, items relating to surgical volume were only included for patients who underwent attempted resection. We then ascertained the items where there was evidence that the specified care had been delivered and summed their mean Delphi scores to create a care-delivered score. The proportional care score was calculated by dividing the care-delivered score by the potential score. Details of the clinical information used to determine eligibility and whether or not the care specified in each item was delivered are shown in Table 7-1.

Table 7-1 : Statements about care for pancreatic cancer deemed to be most important in a Delphi process, patient eligibility criteria and definition of care received

Care Statement	Weight[a]	Eligible[b]	N eligible (% met[c])	Care received
All patients with potentially resectable disease should be referred to an hepatobiliary surgeon[d]	9.3	Non-metastatic	781 (51)	Any[e] referral or consultation with HPB
All patients with technically resectable disease should be offered a resection or valid reason why not	9.2	Potentially resectable	519 (98)	Surgery attempted or valid reason for no surgery
Surgery should be performed by surgeons who perform more than 5 pancreatic surgeries per year	9.0	Resection attempted	366 (43)	Surgeon performed more than 5 surgeries per annum
Tumour resectability should be assessed by a MDT at a tertiary hospital	9.0	Non-metastatic	781 (29)	If MDT prior to attempted surgery or within 40 days of diagnosis if no surgery.
All patients should have a triple phase/ pancreas protocol CT scan for staging	8.9	All patients	1571 (43)	Evidence of pancreas protocol CT
Entry into a clinical trial should be considered for all patients	8.8	All patients	1571 (7)	Clinical trial discussed, considered, offered or participated in a trial
Surgery should take place in tertiary institutions where > 15 resections[f] are performed annually	8.6	Resection attempted	366 (42)	If attempted resection was performed at a hospital where > 11 resections were performed each year[f]
Each patient should have a care-coordinator assigned with an individualised treatment/ clinical plan	8.5	All patients	1571 (22)	Evidence of a navigator, care-plan or nursing referral
Tissue diagnosis should be obtained where possible	8.3	All patients	1571 (80)	Histology or cytology analysis completed
All patients should be presented to a MDT	8.3	All patients	1571 (31)	Evidence of presentation to a MDT
Biliary obstruction should routinely be managed endoscopically in non-resectable patients	8.2	Non-resectable with biliary obstruction	416 (83)	Evidence of endoscopic biliary stent not bypass surgery
All patients should be offered adjuvant therapy post operatively, assuming performance status is adequate	8.1	Resection attempted	366 (67)	Evidence of any adjuvant chemo- or radiation therapy
All patients should be offered psychosocial support	8.0	All patients	1571 (19)	Evidence of referral or consult by psychological services
Pancreatic enzyme replacement therapy should be considered for all patients	7.9	All patients	1571 (22)	Evidence of pancreatic enzyme replacement
All patients should see a medical oncologist	7.9	All patients	1571 (86)	Seen by a medical oncologist or valid reason why not seen
A specialist HPB surgeon should be the initial/primary specialist unless the patient has obvious metastases	7.3	Non-metastatic	781 (19)	HPB was the first specialist seen

Care Statement	Weight[a]	Eligible[b]	N eligible (% met[c])	Care received
All patients should be referred to a dietitian soon after diagnosis	7.3	All patients	1571 (64)	Evidence of referral or consult by dietician
Patients with confirmed metastatic disease should be referred to palliative care	6.0	Metastases	790 (82)	Any[e] evidence of palliative care consult or referral.

[a] Weight: final mean average score of importance following Delphi process

[b] Eligible: patients eligible for care as per classification on clinical staging

[c] % met: percentage of patients eligible who received the item of care.

[d] Hepatobiliary surgeon (HPB) defined as a surgeon who had undergone recognised specialised hepatobiliary surgery training and/or was recognised by their peers as an experienced hepatobiliary surgeon

[e] Any: includes all inpatient records and consultations

[f] Only 3 hospitals from the patterns-of-care study actually supported this number of 15 resections per annum, therefore using previous Australian data and the literature this high-volume classification was amended to hospitals where 11 or more resections were performed each year.

CT: computerized tomography; MDT: multidisciplinary team meeting

Measurement of potential determinants of care

Patient characteristics included: age at diagnosis, sex, Eastern Cooperative Oncology Group (ECOG) performance status, and Charlson comorbidity index.[244] Based on area of residence at the time of diagnosis, each person was allocated a socio-economic index for areas (SEIFA)[245] score and Accessibility/Remoteness Index of Australia (ARIA)[246] category. We grouped the SEIFA score into quintiles and collapsed the ARIA into three groups: major city; inner regional; and outer regional/remote/very remote (hereafter referred to as rural).

Tumour factors included the stage of the tumour following staging investigations. The tumour was staged as potentially resectable or not and also as confined to the pancreas, locally advanced or metastatic.

Health-service factors included the type of specialist first seen and the volume of the facility where the patient was first treated as an inpatient (according to the number of patient presentations in the patterns-of-care study).

Statistical analysis

The proportion of eligible patients who received each item of care was reported and compared across socioeconomic status categories and place of residence; p-values were calculated using Chi-squared tests to determine the statistical significance of any differences.

We used linear regression analyses, with the proportional score as the outcome, to examine variation in the score by patient, tumour and health-service factors. Mean proportional scores for levels of each exposure variable were calculated and beta (β) coefficients reported with 95% confidence intervals (CI). The coefficients can be interpreted as the difference in mean score between patients in a category and those in the reference category. Multivariable models included age, ECOG performance status and comorbidity score.

Survival time was taken from the date of diagnosis until death or date of final follow-up (February 2014). Patients were divided into quartiles based on their proportional care score, Kaplan-Meier graphs generated and log-rank tests used to examine the difference in survival according to score category. We also performed the analysis with the score as a continuous variable, reporting associations per 10% absolute increase in score, using Cox proportional hazard models to adjust for patient factors and clinical stage. The association between the score and survival was investigated further by calculating adjusted hazard ratios for each care score item separately. Analyses were performed within the total patient group and separately among patients who did and did not have

metastases identified on clinical staging. We used Stata 14 (Statacorp, Texas) for analyses. All p-values were two-sided and $p < 0.05$ used as an indication of statistical significance.

Results

In total, 1896 patients were eligible for inclusion in the patterns-of-care study. We were unable to locate medical records for 33, 259 died within one month of diagnosis and 33 were missing staging information, leaving 1571 (83%) for this analysis. On clinical staging, 781 patients (49.7%) had non-metastatic and 790 (50.3%) metastatic disease. Most lived in major cities (n = 1076; 68%) compared to inner regional (n = 338; 22%) and rural areas (n = 157; 10%) and 55% of patients were men (n = 867). Almost three-quarters (n = 1151; 73%) of patients died within one year of diagnosis. The median survival time was 6 months (11 months for those without metastases; 4 months for those with metastases).

Younger patients and those with better performance status had higher care scores than older and less mobile patients (Table 7-2).

Place of residence, area-level socioeconomic status, age, performance status, facility volume and specialist first seen were all associated with the score (Table 7-3). After adjustment the estimated care scores were lower by 11% for patients living in rural areas than for patients living in major cities (β coefficient: -0.11; 95% CI -0.13 to -0.08). Similarly, those living in more disadvantaged areas had estimated care scores lower by 8% than those patients living in the least disadvantaged areas (β -0.08; 95% CI -0.11 to -0.06). Patients presenting to a low volume hospital (<10 presentations annually) had lower care score estimates than those presenting to hospitals with more than 30 presentations (β -0.13; 95% CI -0.15 to -0.11). Care scores were higher for patients whose first specialist was a hepatobiliary surgeon, with patients seeing a general surgeon predicted to have scores lower by 10% (β -0.10; 95% CI -0.13 to -0.08). To further investigate the association between place of residence and care score, models were also adjusted for the volume of the first hospital attended and the first specialist seen. This reduced the adjusted mean score differences between major cities and rural areas (β -0.05; 95% CI -0.08 to -0.03) and between least disadvantaged and most disadvantaged areas (β -0.06; 95% CI -0.08 to -0.03).

Table 7-2: Mean proportional care scores according to patient, tumour and health system characteristics in 1) all patients; 2) patients with no evidence of metastases; and 3) patients with evidence of metastases on clinical staging.

	N (%)	Total mean proportional score (95% CI)				
	All patients (N = 1571)		Non-Metastatic (N = 781)		Metastatic (N = 790)	
Age group (years)						
< 60	307 (20)	0.48 (0.46, 0.50)	145 (19)	0.51 (0.48, 0.53)	162 (21)	0.46 (0.43, 0.49)
60 - 69	417 (27)	0.49 (0.48, 0.51)	221 (28)	0.51 (0.49, 0.53)	196 (25)	0.47 (0.45, 0.50)
70 - 79	471 (30)	0.43 (0.41, 0.44)	233 (30)	0.44 (0.42, 0.46)	238 (30)	0.41 (0.39, 0.43)
80 +	376 (24)	0.34 (0.32, 0.36)	182 (23)	0.32 (0.29, 0.34)	194 (25)	0.36 (0.34, 0.39)
Overall p value[a]		< 0.001		< 0.001		< 0.001
Sex						
Female	704 (45)	0.43 (0.41, 0.44)	350 (45)	0.43 (0.41, 0.45)	354 (45)	0.43 (0.41, 0.45)
Male	867 (55)	0.44 (0.43, 0.45)	431 (55)	0.46 (0.44, 0.48)	436 (55)	0.42 (0.40, 0.44)
Overall p value		0.17		0.01		0.57
Charlson Comorbidity score						
0	680 (44)	0.45 (0.44, 0.46)	342 (44)	0.46 (0.44, 0.48)	338 (44)	0.44 (0.42, 0.46)
1	498 (32)	0.43 (0.42, 0.44)	242 (31)	0.44 (0.41, 0.46)	256 (33)	0.42 (0.40, 0.45)
2	370 (24)	0.43 (0.41, 0.44)	194 (25)	0.43 (0.40, 0.46)	176 (23)	0.42 (0.39, 0.45)
Overall p value[a]		0.05		0.07		0.52
Performance Status						
0	431 (27)	0.48 (0.47, 0.50)	270 (35)	0.49 (0.47, 0.51)	161 (20)	0.47 (0.45, 0.50)
1	538 (34)	0.46 (0.45, 0.47)	250 (32)	0.47 (0.45, 0.49)	288 (36)	0.45 (0.43, 0.47)
2+	373 (24)	0.39 (0.37, 0.40)	152 (19)	0.37 (0.34, 0.40)	221 (28)	0.40 (0.38, 0.42)
Not stated	229 (15)	0.36 (0.33, 0.38)	109 (14)	0.38 (0.35, 0.41)	120 (15)	0.34 (0.30, 0.37)
Overall p value[a]		< 0.001		< 0.001		< 0.001
Place of residence						
Major City	1076 (68)	0.45 (0.44, 0.46)	548 (70)	0.46 (0.45, 0.47)	528 (67)	0.45 (0.43, 0.46)
Inner Regional	338 (22)	0.40 (0.38, 0.42)	159 (20)	0.43 (0.40, 0.46)	179 (23)	0.38 (0.35, 0.40)
Rural[b]	157 (10)	0.37 (0.34, 0.40)	74 (9)	0.36 (0.32, 0.40)	83 (11)	0.38 (0.34, 0.42)
Overall p value[a]		< 0.001		< 0.001		< 0.001

	N (%)	Total mean proportional score (95% CI)				
	All patients (N = 1571)		Non-Metastatic (N = 781)		Metastatic (N = 790)	
Socio-economic status-quintiles						
Least disadvantaged	266 (17)	0.48 (0.46, 0.50)	138 (18)	0.49 (0.47, 0.52)	128 (16)	0.47 (0.44, 0.50)
2	327 (21)	0.45 (0.43, 0.47)	160 (20)	0.46 (0.44, 0.49)	167 (21)	0.45 (0.42, 0.47)
3	322 (21)	0.42 (0.40, 0.44)	160 (20)	0.42 (0.39, 0.44)	162 (21)	0.42 (0.39, 0.44)
4	338 (22)	0.42 (0.40, 0.43)	169 (22)	0.42 (0.40, 0.45)	169 (21)	0.41 (0.38, 0.43)
Most disadvantaged	318 (20)	0.41 (0.39, 0.43)	154 (20)	0.43 (0.40, 0.46)	164 (21)	0.39 (0.36, 0.42)
Overall p value[a]		< 0.001		< 0.001		< 0.001
Clinical Stage of disease						
Confined to pancreas	227 (14)	0.52 (0.50, 0.54)				
Locally advanced	554 (35)	0.52 (0.51, 0.53)				
Metastatic	790 (50)	0.48 (0.46, 0.49)				
Overall p value[a]		0.03				
Tumour site						
Head/neck[c]	1024 (72)	0.46 (0.44, 0.47)	643 (85)	0.45 (0.44, 0.47)	381 (57)	0.46 (0.44, 0.48)
Body	134 (9)	0.43 (0.40, 0.46)	37 (5)	0.42 (0.37, 0.48)	97 (15)	0.43 (0.40, 0.47)
Tail	144 (10)	0.40 (0.38, 0.43)	44 (31)	0.43 (0.38, 0.48)	100 (15)	0.39 (0.36, 0.43)
Multiple sites	119 (8)	0.42 (0.39, 0.45)	34 (5)	0.44 (0.39, 0.49)	85 (13)	0.41 (0.38, 0.45)
Overall p value[a]		0.002		0.63		0.002
First facility volume						
> 30	756 (49)	0.49 (0.48, 0.50)	415 (54)	0.49 (0.48, 0.51)	341 (45)	0.48 (0.47, 0.50)
29 - 10	460 (30)	0.42 (0.41, 0.44)	236 (31)	0.41 (0.39, 0.43)	224 (29)	0.44 (0.42, 0.46)
< 10	315 (21)	0.33 (0.32, 0.35)	119 (15)	0.35 (0.32, 0.38)	196 (26)	0.33 (0.30, 0.35)
Overall p value[a]		0.002		0.63		0.002
First specialist seen						
Hepatobiliary surgeon	234 (15)	0.55 (0.53, 0.57)	146 (19)	0.58 (0.56, 0.60)	88 (11)	0.51 (0.47, 0.54)
Gastroenterologist	402 (26)	0.44 (0.43, 0.46)	240 (31)	0.44 (0.42, 0.46)	162 (21)	0.45 (0.43, 0.48)
General Surgeon	501 (32)	0.43 (0.42, 0.44)	289 (37)	0.42 (0.40, 0.44)	212 (27)	0.45 (0.43, 0.47)
Other[d]	434 (28)	0.37 (0.35, 0.38)	106 (14)	0.35 (0.32, 0.38)	328 (42)	0.37 (0.35, 0.39)
Overall p value[a]		< 0.001		< 0.001		< 0.001

CI – confidence interval

[a] p-value calculated using one-way analysis of variance (ANOVA); [b] Includes outer regional, remote and very remote ; [c] Includes tumour in uncinate process;

[d] Includes oncologists and palliative care physicians.

Table 7-3: Associations between patient, tumour and health service characteristics and proportional care scores[a] in 1) all patients; 2) patients with no evidence of metastases; and 3) patients with evidence of metastases on clinical staging.

	β coefficient (95% confidence interval)					
	Crude	Adjusted[b]	Crude	Adjusted[b]	Crude	Adjusted[b]
	All patients (N = 1571)		Non-metastatic (N = 781)		Metastatic (N = 790)	
Age group (years)						
< 60	ref	ref	ref	ref	ref	ref
60 - 69	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.03, 0.04)	0.01 (-0.02, 0.04)	0.01 (-0.03, 0.05)	0.00 (-0.03, 0.04)
70 - 79	-0.06 (-0.08,-0.03)	-0.05 (-0.08, -0.03)	-0.06 (-0.10, -0.03)	-0.05 (-0.08, -0.02)	-0.05 (-0.09, -0.02)	-0.06 (-0.09, -0.03)
80 +	-0.14 (-0.17, -0.12)	-0.13 (-0.15, -0.10)	-0.19 (-0.23, -0.16)	-0.16 (-0.20, -0.13)	-0.10 (-0.13, -0.06)	-0.10 (-0.13, 0.06)
Overall p value, p trend	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001
Sex						
Female	ref	ref	ref	ref	ref	ref
Male	0.12 (-0.01, 0.03)	-0.01 (-0.02, 0.01)	0.03 (0.01, 0.06)	0.01 (-0.01, 0.03)	-0.01 (-0.03, 0.08)	-0.03 (-0.05, -0.00)
Overall p value	0.17	0.34	0.01	0.40	0.57	0.03
Charlson Comorbidity score						
0	ref	ref	ref	ref	ref	ref
1	-0.02 (-0.04, 0.00)	-0.01 (-0.03, 0.01)	-0.03 (-0.06, 0.00)	-0.00 (-0.03, 0.02)	-0.01 (-0.04, 0.16)	-0.01 (-0.03, 0.02)
2	-0.02 (-0.05, -0.00)	-0.01 (-0.03, 0.01)	-0.03 (-0.06, -0.00)	-0.01 (-0.04, 0.02)	-0.02 (-0.05, 0.02)	-0.01 (-0.04, 0.02)
Overall p value, p trend	0.05, 0.02	0.64, 0.38	0.07, 0.03	0.88, 0.63	0.52, 0.27	0.89, 0.66
Performance Status						
0	ref	ref	ref	ref	ref	ref
1	-0.02 (-0.05, -0.00)	-0.01 (-0.03, 0.01)	-0.02 (-0.05, 0.01)	-0.01 (-0.04, 0.02)	-0.02 (-0.06, -0.01)	-0.01 (-0.04, 0.02)
2+	-0.10 (-0.12, -0.07)	-0.06 (-0.08, -0.03)	-0.12 (-0.16,-0.09)	-0.06 (-0.09, -0.03)	-0.07 (-0.11, -0.04)	-0.05 (-0.08, -0.02)
Not stated	-0.13 (-.015, -0.10)	-0.09 (-0.12, -0.06)	-0.11 (-0.15, -0.07)	-0.07 (-0.11, -0.03)	-0.14, (-0.18, -0.10)	-0.11, (-0.15, -0.07)
Overall p value, p trend	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001
Place of residence						
Major City	ref	ref	ref	ref	ref	ref
Inner Regional	-0.05 (-0.07,-0.03)	-0.06 (-0.08, -0.04)	-0.03 (-0.06, 0.00)	-0.03 (-0.06, -0.00)	-0.07, (-0.10, -0.04)	-0.08 (-0.11, -0.05)
Rural[c]	-0.08 (-0.11, -0.05)	-0.11 (-0.13, -0.8)	-0.10 (-0.14, -0.06)	-0.11 (-0.15, -0.08)	-0.07 (-0.11, -0.03)	-0.09 (-0.13, -0.06)
Overall p value, p trend	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001

	β coefficient (95% confidence interval)					
	Crude	Adjusted[b]	Crude	Adjusted[b]	Crude	Adjusted[b]
	All patients (N = 1571)		Non-metastatic (N = 781)		Metastatic (N = 790)	
Socio-economic status-quintiles						
Least disadvantaged	ref	ref	ref	ref	ref	ref
2	-0.03 (-0.06,-0.00)	-0.03 (-0.06,-0.01)	-0.03 (-0.07, 0.01)	-0.04 (-0.07, -0.00)	-0.03 (-0.07,0.01)	-0.03 (-0.07,0.01)
3	-0.07 (-0.10, -0.04)	-0.07 (-0.10, -0.04)	-0.08 (-0.12, -0.04)	-0.08 (-0.12, -0.05)	-0.06 (-0.10, -0.02)	-0.06 (-0.10, -0.02)
4	-0.07 (-0.10, -0.04)	-0.08 (-0.11, -0.05)	-0.07 (-0.11, -0.03)	-0.08 (-0.12, -0.05)	-0.07 (-0.11, -0.03)	-0.08 (-0.12, -0.04)
Most disadvantaged	-0.07 (-0.10, -0.05)	-0.08 (-0.11, -0.06)	-0.06 (-0.10, -0.02)	-0.07 (-0.10, -0.03)	-0.08 (-0.12, -0.04)	-0.10 (-0.13, -0.06)
Overall p value, p trend	< 0.001, < 0.001	< 0.001, < 0.001	0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001
Clinical Stage of disease						
Confined to pancreas	ref	ref				
Locally advanced	-0.02 (-0.04, 0.01)	-0.02 (-0.04, 0.01)	n/a	n/a	n/a	n/a
Metastatic	-0.03 (-0.06, -0.01)	-0.02 (-0.04, 0.00)				
Overall p value, p trend	0.03, 0.01	0.26, 0.14				
First facility volume						
> 30	ref	ref	ref	ref	ref	ref
29 - 10	-0.06,(-0.08, -0.05)	-0.06 (-0.08, -0.04)	-0.08 (-0.11, -0.06)	-0.07 (-0.10, -0.05)	-0.04 (-0.07, -0.02)	-0.04 (-0.07, -0.02)
< 10	-0.16 (-0.18, -0.13)	-0.13 (-0.15, -0.11)	-0.14 (-0.18, -0.11)	-0.10 (-0.13, -0.07)	-0.16 (-0.19, -0.13)	-0.15 (-0.17, -0.12)
Overall p value, p trend	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001	< 0.001, < 0.001
First specialist seen						
Hepatobiliary surgeon	ref	ref	ref	ref	ref	ref
Gastroenterologist	-0.11 (-0.14, -0.08)	-0.09 (-0.11, -0.06)	-0.14 (-0.18, -0.11)	-0.12 (-0.15, -0.09)	-0.05 (-0.10, -0.01)	-0.03 (-0.07, 0.01)
General Surgeon	-0.12 (-0.15, -0.10)	-0.10 (-0.13, -0.08)	-0.16 (-0.19, -0.13)	-0.13 (-0.16, -0.10)	-0.06 (-0.10, -0.02)	-0.05 (-0.09, -0.01)
Other	-0.19 (-0.21 , -0.16)	-0.14 (-0.16, -0.11)	-0.23 (-0.27, -0.19)	0.17 (-0.21, -0.13)	-0.14 (-0.18, -0.10)	-0.10 (-0.14, -0.06)
Overall p value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

[a] The higher the proportional care score the higher the quality of care.

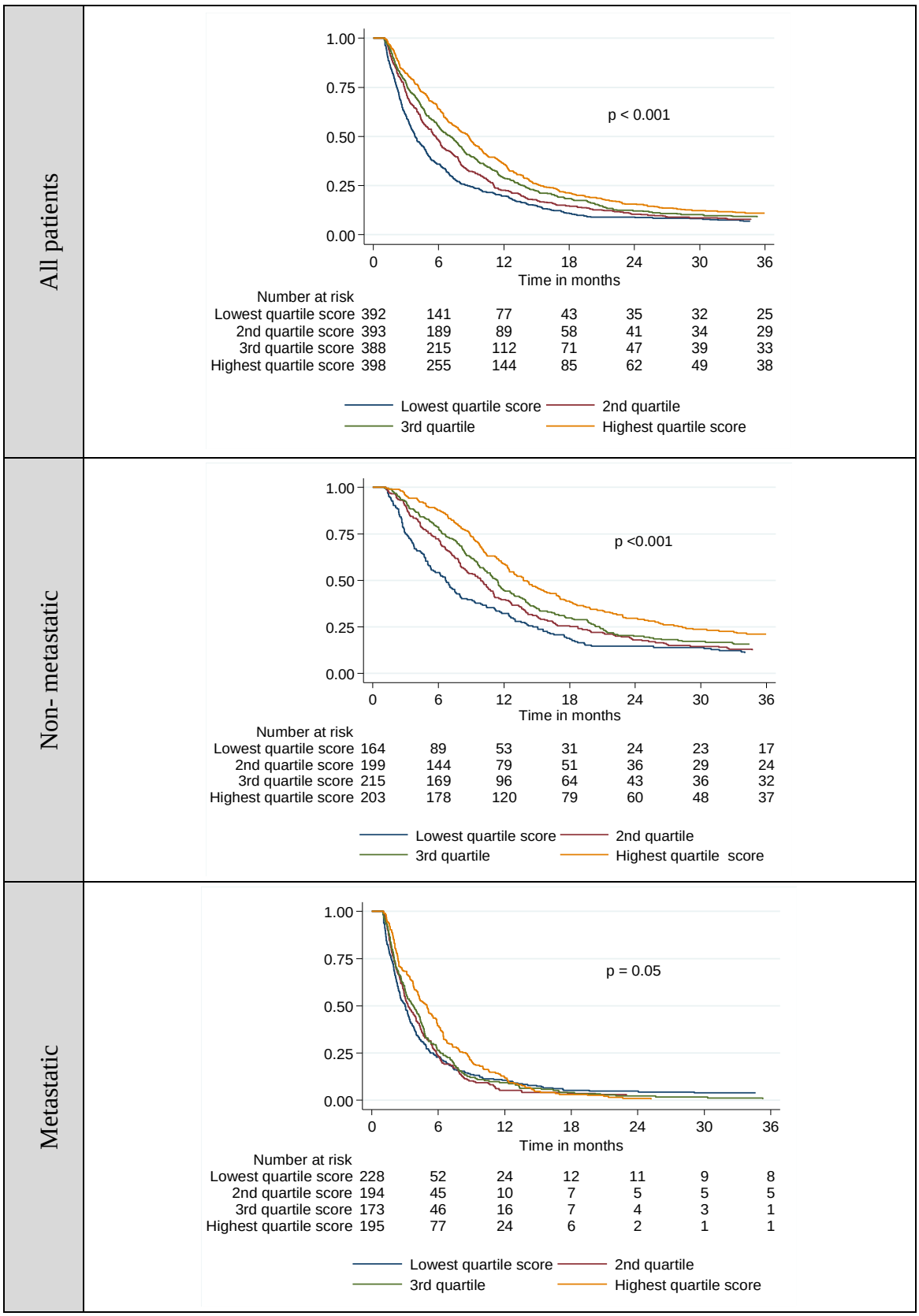
[b] Adjusted for age at diagnosis (< 60, 60 - 69, 70 - 79, 80 + years); performance status(0, 1, 2+, not stated); and Charlson comorbidity index score (0, 1, 2+)

[c] Includes patients in outer regional, remote and very remote areas

For patients clinically staged with non-metastatic disease the factors most strongly associated with higher care scores were being first seen by a hepatobiliary surgeon compared to a general surgeon (β -0.17; 95% CI -0.21 to -0.13), living in a major city rather than a rural area (β -0.11; 95% CI -0.15 to -0.08) and being less than 60 years of age compared to 80 years or older (β -0.16; 95% CI -0.20 to -0.13). For patients diagnosed with metastatic disease, being seen at a higher volume facility (β -0.15; 95% CI -0.17 to -0.12) and having better performance status (β -0.11; 95% CI -0.15 to -0.07) were most strongly associated with the quality of care.

Regarding individual items of care, a small proportion of patients were presented to multidisciplinary teams (MDTs) (31%), received psychosocial support (19%), participated in clinical trials (7%) and were first seen by a hepatobiliary surgeon (19%) (Table 7-1). Most eligible patients were offered a resection (or had a valid reason why not) (98%), had a tissue diagnosis (80%), saw a medical oncologist (86%) and were referred to palliative care (82%). There were significant differences for patients by place of residence and area-level socioeconomic status. For example, 41% of patients in rural areas were referred to a hepatobiliary surgeon compared with 53% of patients in metropolitan areas (Appendix G: Table 9-6 and Table 9-7).

Patients with scores in the highest quartile had an estimated median survival of 8 months, double that for those with scores in the lowest quartile. Median survival for patients with non-metastatic disease in the highest and lowest score quartiles respectively was 14 and 7 months; in those with metastatic disease it was 5 and 3 months (Figure 7-1).



P values calculated using log-rank test to test the equality of survivor functions across quartiles of proportional care score groups.

Figure 7-1: Kaplan-Meier survival curves by quartiles of proportional care score for all patients, patients with non-metastatic disease and patients with metastatic disease on clinical staging.

After adjusting for age, performance status, comorbidities and clinical stage, each 10% absolute increase in proportional care score was associated with a statistically significant 6% reduction in the risk of dying (HR 0.94; 95% CI: 0.91 to 0.97) (Table 7-4).

Table 7-4: Association between total care score and survival by stage of pancreatic cancer at diagnosis.

	Number of patients	Hazard ratio[HR] (95% confidence interval)	
		HR	Adjusted HR [a]
All patients	1571	0.90 (0.87, 0.93)	0.94 (0.91, 0.97)
p value		< 0.001	< 0.001
Non-metastatic	778	0.87 (0.83, 0.91)	0.91 (0.87, 0.95)
p value		< 0.001	< 0.001
Metastatic	790	0.95 (0.91, 0.98)	0.95 (0.91, 0.99)
p value		0.006	0.013

HRs refer to the change in the risk of dying associated with a 10 percentage point increase in care score.

[a] HR adjusted for age group (<60, 60-69, 70-79, 80+), performance status (0, 1, 2+, not stated), Charlson comorbidy score (0, 1, 2+), clinical stage (confined, locally advanced, metastatic).

This was more marked for patients who were diagnosed with non-metastatic disease than for those diagnosed with metastatic disease with adjusted HRs of 0.91 (95% CI: 0.87 to 0.95) and 0.95 (95% CI: 0.91 to 0.99), respectively. Individual care score items that were statistically significantly associated with survival included having a diagnostic tissue sample collected (HR 0.66; 95% CI: 0.57 to 0.77), being offered adjuvant chemotherapy (HR 0.43; 95% CI: 0.33 to 0.56), being referred to a hepatobiliary surgeon if potentially resectable (HR 0.82; 95% CI: 0.69 to 0.96), being presented to an MDT (HR 0.86; 95% CI: 0.77 to 0.96), being offered psychosocial support (HR 1.24; 95% CI: 1.09 to 1.12), having evidence of pancreatic enzyme replacement therapy (HR 0.83; HR 95% CI: 0.73 to 0.94) and, if diagnosed with metastatic disease, evidence of referral to palliative care (HR 1.42; 95% CI: 1.17 to 1.74) (Appendix G: Table 9-8).

Discussion

We found that the quality of care of patients with pancreatic cancer differs according to their age, where they live and the volume of the hospital at which they first present. We also found that the quality of care is associated with improved survival and that this association is strongest for patients clinically staged with non-metastatic pancreatic cancer, where there is more scope for treatment to make a survival difference.

Previous studies have found that receipt of surgery, chemotherapy and palliative care is influenced by patients' age, education, place of residence, race and marital status.[10, 12, 13] By examining a composite measure of care, including a broad range of factors, we have shown that age and performance status influence the overall quality of care received. While this is unsurprising, it is important that age alone is not seen as a barrier to delivery of high quality care. The more concerning finding is that care differs according to place of residence and area-level socioeconomic status. This is at least partially mediated by access to specialists and care in a high volume centre, suggesting that interventions to ensure all patients are managed by high-volume teams could improve the quality of care.

Our analysis of individual care items showed that the proportion of people who received the recommended care was particularly low for items relating to where and by whom treatment was received. For example, less than a third of patients had evidence of MDT referral, only half of potentially resectable patients were referred to a hepatobiliary surgeon, and clinical trial involvement was only rarely considered, even though these factors have consistently been found to influence quality of care.[93-95] These aspects of care were particularly poorly met for patients living in more rural areas. Distance presents distinct challenges in Australia, [303-305] but these should not be insurmountable. Studies have shown that a multilevel approach (which could involve holding telemedicine MDTs and formalising referral relationships between regional and metropolitan centres) can improve outcomes.[306]

Patients with lower care scores had poorer survival, consistent with previous observations that delivery of high quality care improves survival.[307-309] This association was stronger for patients diagnosed with non-metastatic disease, where there is more scope to influence survival by ensuring adequate staging, surgery in high-volume centres and access to adjuvant chemotherapy. For patients with metastatic disease a focus on quality-of-life indicators is arguably more important and this should be explored in future studies of care quality.

Some individual care items were associated with higher estimates of dying if the care was received, such as patients should be "offered psychosocial support", "patients with metastatic disease should be referred to palliative care" and "patients with technically resectable disease should be offered a resection or a valid reason for no surgery". Receipt of psychosocial and palliative care is more likely to occur as expected survival time shortens which is likely to explain the results (i.e. reverse causation). The item regarding resection was classified as having been delivered if a valid reason for the resection not being offered was recorded. This applied to 28% of patients eligible for resection; the reasons for no surgical attempt were older age, comorbidity and poor performance

status, all of which are associated with poor survival. When these items were omitted from the overall care score, the risk of dying was 2% lower for each 10 percentage point increase in care score.

This study is comprehensive, reasonably large and population-based and is the first Australian study to consider the overall quality of care in a single score. Nevertheless, it does have some limitations. Firstly, different weights for the care items may have been obtained if the mix of specialists who participated in the Delphi study had been different. Secondly, the Delphi study highlighted the importance of communication between patients and clinicians. This cannot be adequately captured through review of medical records so could not be incorporated into our score, but might have influenced decisions regarding care. Thirdly, some patients may have been incorrectly classified as resectable which caused them to be ineligible (or eligible) for care items, with appropriate care (or not) delivered. Finally, while we controlled for age, performance status and comorbidities this may not have completely accounted for confounding by patient factors.

In conclusion, this population-based study provides evidence that place of residence and other factors influence the quality of care received by Australian patients with pancreatic cancer and that survival gains can be realised by ensuring optimal care is provided. Systems need to be implemented to ensure delivery of equitable care for all Australian patients with pancreatic cancer.

Chapter 8: Discussion

The research included in this thesis provides a comprehensive understanding of the management of patients diagnosed with pancreatic cancer in QLD and NSW. It has also identified indicators of optimal care, and factors associated with receipt of high-quality care.

This final chapter summarises the contribution and significance of the work contained in this thesis, compares the findings with those from other studies and discusses the strengths and limitations of the research. The directions for further investigation and implications of the results conclude the chapter and thesis.

8.1. OVERVIEW OF FINDINGS

The findings from a Delphi process used to identify indicators of care that clinicians deem important in providing optimal care for patients with pancreatic cancer were described in Chapter 4. Approximately a quarter of the items derived from the initial open-ended question related to presentation and staging, and over a third of items related to when and where care should occur and which specialists should be involved. All items derived were reflected in the State of Victoria's Department of Health and Human Services optimal care pathway,[95] including the importance of communication. Consensus was reached for many items, such as the need for patients to be assessed by a hepatobiliary surgeon, for surgery to occur in a high-volume centre and the importance of management by a multidisciplinary team, although there was some variability according to the specialty of the clinician. Surgeons tended to prioritise surgical factors, while other clinicians considered supportive care to be of higher importance. The mean scores of items for which consensus was reached and for which information was available in the medical records were used to calculate a quality-of-care score as described in Chapter 7.

Chapter 5 described the cohort of patients included in the patterns-of-care study and provided a broad overview of their management. Almost 60% of patients were diagnosed with metastatic disease and approximately three-quarters of tumours affected the head, neck or uncinate process. Approximately 20% of patients underwent an attempted resection but this was not completed for 25% of these, so the proportion resected was 15%. Approximately 75% of patients who underwent a complete resection received adjuvant chemotherapy, and for the 43% of patients in whom the resection was aborted or not attempted, palliative chemotherapy was their primary treatment modality. Only 8% of patients received radiation therapy in either the adjuvant or palliative setting. The median survival was 4.5 months for the entire cohort.

Chapter 6 focused on determinants of receipt of surgery and survival for patients who were not found to have metastatic disease during the initial staging investigations. Patients living in more remote areas and those not reviewed by a hepatobiliary surgeon were less likely to be offered

surgery. Patients presented at a MDT meeting were also less likely to be assessed as having a potentially resectable tumour than those with no evidence of a MDT review. Along with age, comorbidities and tumour stage, increasing remoteness of residence was associated with poorer survival.

Chapter 7 described the construction of a quality-of-care score based on indicators derived from the Delphi process. We showed that quality-of-care scores were lower for older patients, those with poorer performance status and those living in rural areas compared with major cities. Rural patients were less likely to be assessed by an MDT or hepatobiliary surgeon and less likely to have evidence of psychosocial and palliative care support. Patients who first presented to a hospital with a high pancreatic cancer case load had higher scores than those presenting at low case-volume hospitals. Higher quality-of-care scores were associated with improved survival, particularly for patients diagnosed with non-metastatic disease.

In summary, the Delphi process showed that most clinicians agree on the importance of highly expert care in the management of patients with pancreatic cancer. However the patterns-of-care study illustrated that not all patients receive this high standard of care. As expected, survival was poor, especially for patients diagnosed with metastatic disease, but was also worse for patients living in more rural areas. There was inequitable access to surgical staging, and the overall quality-of-care score varied by region of residence. This work provides impetus for changes in policy and practice to ensure that all patients diagnosed with this lethal disease have optimal care.

8.2. COMPARISON OF FINDINGS WITH PREVIOUS RESEARCH

8.2.1. Patient cohort

The demographic characteristics of the patient cohort in this study were consistent with those in other Australian and international studies. The median age of 71 years and the proportion male (54%) match reports from the United States SEER data[274] and the Australian cancer registry data in 2010.[275] With respect to geographical location, the distribution of the cohort is almost identical to that of the Australian population,[276] suggesting that the risk of pancreatic cancer does not differ appreciably according to remoteness of residence. The proportion diagnosed with metastatic disease (58%) is comparable to other recent international reports (range 46% - 59%).[10, 123, 221] The tumour location, with 72% being in the head of the pancreas, is also consistent with other reports (range 69% – 79%).[33, 106, 107, 294]

8.2.2. Management of pancreatic cancer patients

Median survival for the cohort was 4.5 months and 22% survived at least one-year following diagnosis which is consistent with recent international and Australian registry data. Although not a direct comparison within a single population over time, data from the United States, the United Kingdom and NSW indicates that survival rates have improved slightly over the past few decades (1-year relative survival from approximately 12% in the 1980s to 20-21% in 2010, 5-year survival from 3% in 1985 to 7% for 2010).[34, 39, 60] Improvements in survival have been mainly observed for patients diagnosed with non-metastatic disease, particularly for patients with a completed resection of their disease.[91, 294]

We observed that 15% of patients underwent complete resection of their primary tumour. Most previous studies have reported 10-15%,[10, 13, 62, 216] with no obvious trends over time or by country. Previous Australian population-based investigations found that 11% of patients diagnosed during 2002-2003 in Victoria and 13% of patients diagnosed in Queensland during 2009-2011 underwent surgical resection of their tumour.[107, 192] Thus we report a small increase, although whether this is a real increase or is due to random variation is unclear.

Almost a third of patients with potentially resectable disease in our series did not undergo resection of their tumour (31%). This included 58% of patients with stage I disease which is slightly lower than the 64% reported for a series of patients diagnosed in 2004 in the United States.[106] Most patients (94%) in our cohort with Stage I disease who did not undergo attempted surgery had a valid reason for not progressing to surgery. These included age and or comorbidities (61%), refusal (24%) and poor performance status (8%). A reason was not recorded for only three patients (6%). In the United States report, age and comorbidities accounted for 22% of those who did not have surgery and 6% refused, but for 72% the reasons were unknown.

We found that approximately 25% of attempted resections were not completed due to the discovery of metastases or disease that invaded arteries. A Victorian population-based study indicated that 32% had an attempted resection that was not completed and was converted to a biliary bypass procedure due to previously undiagnosed unresectable disease.[107] The high number of incomplete resections found in both studies may indicate inadequate staging for patients with borderline resectable disease, exacerbated by the lack of consensus guidelines available regarding the classification of resectability. It may also suggest that surgeons are more willing to attempt resections given the improvements in surgical techniques that have occurred.[279]

Adjuvant chemotherapy is current standard of care, as it was at the time the patients in this study were diagnosed. We found that 76% of patients received adjuvant chemotherapy following

completed resections, the range reported in other international and Australian studies, using data from between 2000 and 2010, is between 40% and 83%.[10, 18, 62] Only two studies reported rates of 75% or more, both conducted using more recent data (2005-2010).[10, 216] An Australian report from 2000-2001 showed that approximately half of the patients received adjuvant chemotherapy following resection.[18] Since the time of this previous Australian data the ESPAC-1 trial,[157] CONKO-001 trial[143] and a meta-analysis[147] have been published supporting the use of adjuvant chemotherapy, which likely accounts for the high proportion of use that we have identified.

Less than half of the patients in our study who did not undergo a resection of their primary lesion received chemotherapy (43%). The range in previous patterns-of-care studies was 20% to 42% but comparisons for this group are problematic due to differences in the patient groups included and differences in reporting. Studies with low use of palliative chemotherapy may have been biased due to the use of administrative data which notoriously under-reports chemotherapy use. The previous Victorian patterns-of-care study reported that 32% of patients treated with palliative intent received chemotherapy[18] so our data suggest some increase in use of palliative chemotherapy in the intervening decade. Recent trials of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX)[153] and nab-paclitaxel (Abraxane)[310] therapy have shown statistically significant survival and quality-of-life benefits over gemcitabine which has been the standard of care since the beginning of the century. Following these trial results the proportions of patients receiving chemotherapy might have changed since we completed our data collection, and this is likely to continue to increase as more evidence unfolds.

There is limited evidence to suggest that radiotherapy therapy improves the outcomes of patients with pancreatic cancer. Nevertheless, guidelines from the United States based on low-level evidence and expert opinion suggest that radiation could be used in the following contexts: 1) as post-operative adjuvant therapy; 2) for inoperable stage I-II pancreatic cancers; 3) for locally advanced stage III cancers; and 4) for symptomatic disease requiring palliation.[6] An Australian report based on these guidelines estimated that 49% of patients in Australia should receive radiation therapy at some point during their disease course, although this did not allow for poor performance status.[304] We found that only 8% of patients received radiation therapy. We did not investigate factors associated with receipt of radiotherapy, but this low proportion almost certainly reflects the lack of high-quality evidence to support its use in most patients. The role of radiation in the treatment of patients with pancreatic cancer warrants further investigation to provide higher level evidence regarding its use.

International and Australian recommendations are that all patients, especially those with localised disease, should be managed by a MDT.[6, 94, 159, 180] We found evidence of review by a MDT for 28% of all patients in our cohort and for 34% of those without metastatic disease. While this remains low, it is a significant improvement over the 7% reported in the Victorian study from 2000-2001.[18] There are few international data with which to compare our results, largely because most studies from the United States use administrative datasets which do not include information about MDT review. Further, the definition of a MDT varies. Nevertheless, a recent report from the Netherlands reported that 64% of all patients with suspected pancreatic or periampullary cancer were discussed within a MDT, perhaps indicating more developed multidisciplinary pathways or more robust documentation of MDT review.[126]

8.2.3. Associations with access to cancer-directed therapies

Equitable access to surgery, performed in a highly-skilled setting, has been suggested as the key to reducing variation in long-term survival for patients with pancreatic cancer.[123, 146] We found that older patients, and those with poorer performance status or more comorbidities were less likely to have surgery than younger, more active patients or those with fewer comorbidities. These results are consistent with the literature.[10, 12, 13, 213, 214, 216, 221] Pancreatic resection causes serious morbidity and five-year survival in surgical patients is less than 20%,[34, 113, 143] so it is appropriate that functional status and fitness for surgery influences decisions about resection. However, these factors should not necessarily influence the staging classification of the tumour as resectable or not. Our observation that they were associated with resectability might indicate inadequate staging investigations, potentially denying patients the opportunity to make fully informed decisions about their treatment.

We observed that location of residence in a major city and in a less disadvantaged area, compared with rural locations or areas of high disadvantage, was significantly associated with improved access to surgery. Literature from the Unites States and Canada all confirm similar significant findings.[13, 210, 216] In Australia, a recent Queensland government population-based report on pancreaticoduodenectomy found that 15% of patients living in affluent areas diagnosed with pancreatic cancer between 2009 and 2011 received pancreaticoduodenectomies compared with 12% of patients living in disadvantaged areas.[192] Our findings that the case volume of the hospital to which the patient first presented influences access to surgery is consistent with the international literature,[13, 131, 212] and it is likely that this mediates the association with location of residence.

We found that higher global quality-of-care scores were associated with improved survival. There are few studies with which to compare this finding, but a study from the Unites States found that

pancreatic cancer patients whose care was compliant with clinical guidelines had significantly reduced odds of dying over the five-year study period (OR 0.64; 95% CI: 0.53 – 0.77).[222] Scores were also higher for patients living in metropolitan or less disadvantaged areas than those living in more rural or disadvantaged areas. This is likely to be explained by differences in access to specialist services at high-volume centres.

Overall, the management of Australian pancreatic cancer patients appears to be of higher quality than that reported in other developed countries. This likely reflects the more contemporary nature of our data and our careful review of medical records. We have shown that a large proportion of patients received recommended adjuvant therapy and that the overall survival of the cohort is slightly improved from previous population-based international and Australian reports, but we have also shown that there is evidence of inequitable access to care. There is a paucity of other Australian data; therefore, robust analysis of temporal change is not possible. These comprehensive data will provide a baseline with which future trends can be compared.

8.3. RESEARCH STRENGTHS AND LIMITATIONS

The patterns-of-care study on which this research is based is the most extensive study ever completed for patients with pancreatic cancer in Australia. Just over half of the population of Australia resides in NSW or QLD; the findings are likely to be broadly generalisable to other states, although there may be some disparities due to the different geographic dispersion in the smaller states and territories not included in this study. The findings are also likely to be transferrable to other countries with similar health care systems and geographical population dispersion. The nurses who collected data were carefully trained to ensure standardisation of the collection. The data were also more comprehensive and complete than that obtained from administrative datasets.[283, 284] Much of the research performed that has not depended on these administrative datasets has been in single centres or restricted to clinical trial settings, generating results that are not generalisable to the wider population. Accessing the medical records required considerable investment of time in navigating human ethics and governance requirements, in addition to the challenges related to geographical dispersion of the records. Increased investment in linkage of health data may overcome some of these issues, although regulatory requirements continue to be inconsistent across state jurisdictions. We captured data for 96% of all patients diagnosed during the study period, ensuring minimal bias, although the completeness of records may have varied according to patient or health-system characteristics.

Despite the noted strengths, this study does have some limitations. The data are now already five years old due to constraints relating to access to registry data, obtaining ethical and administrative

approvals from over 100 hospitals and the management of a large dataset. With rapidly advancing technology, new chemotherapy regimens and updated staging and treatment guidelines since the inception of the study, patterns of care may have changed since the data were collected. The study was also relatively small with approximately 2000 participants, reducing the statistical power to detect associations in some patient subgroups.

The data used in this study were abstracted from medical records which vary in their completeness. The absence of information about a particular care item did not necessarily mean that the care did not occur, but just that it was not recorded. Information about discussions with patients was often not documented. Thus, we may have classified a care item as inappropriately not delivered, but the decision may have been made by the patient after consultation with the treating clinician.

In developing the quality-of-care score, different items of care or weights for the care items may have been obtained if a different mix of clinical specialists had participated in the Delphi process. The opinions of patients may have also enriched the final care items and their weights. Nevertheless, the final quality-of-care score was shown to be associated with survival indicating its relevance and validity for patients with pancreatic cancer. However, as most patients present with advanced disease and only a small proportion undergo surgical resection, quality-of-life or other patient-reported outcomes may be better indicators of quality of care than survival.

The classification of tumours as resectable or not may have affected the results, particularly those reported in Chapter 6. We did not have centralised assessment of resectability and were therefore dependent on the decisions of the clinicians as documented in the medical record. At the time the patients were diagnosed, criteria for resectability were unclear and changing, making the decision somewhat subjective. To obviate this problem our classification of resectability included subclassifications (tumour confined to pancreas; tumour locally advanced but resectable; tumour locally advanced and unresectable; and metastatic). We also captured TNM stage where possible enabling alternate staging associations to be estimated and reducing the impact of potential incorrect resectability classifications.

8.4. FUTURE RESEARCH AND IMPLICATIONS

These results provide clear indications that while expert high-level care is provided to some patients, not all Australian pancreatic cancer patients receive care that is consistent with guidelines or the consensus opinion of expert clinicians. There is evidence of inequity in access to cancer-directed therapies, with patients living further from metropolitan centres particularly susceptible to a lack of specialist services and high quality multidisciplinary care.

8.4.1. Future research

Although we have generated sufficient evidence to support immediate changes in policy and practice, this work has identified some gaps in knowledge. Firstly, we have shown that rurality of residence influences whether or not patients are classified as having potentially resectable disease. This is a critical point in the care pathway, as resection of the tumour is currently the only curative treatment modality. Given the potential importance of this finding, further research is needed to understand this geographic variability in classification of resectability. Ideally an audit of patients' records should occur and the staging investigations of all patients without metastatic disease should be reviewed by a centralised audit team to assess the accuracy of surgical decisions. Further research focussed specifically on multidisciplinary care to identify the ideal composition of the team, who should be presented and at what point/s during their course of disease, and barriers to access would increase knowledge in this area. Secondly, we have focussed on survival as the key patient outcome. While improving survival remains the ultimate goal of therapy, the effect of quality of care on patient-reported outcomes such as quality of life, anxiety and distress should also be considered. It is also important that consumers provide input into a care score before it is widely implemented to monitor management. Consumers should be involved in a separate Delphi process and also asked to score the items identified by clinicians. The quality-of-care score could be advanced by testing its validity and impact in other settings. The score is likely to be widely generalisable due to the accessibility of item components in medical records.

The establishment of a population-based clinical registry would enable a tissue bank to support investment in improved treatment.

8.4.2. Translating findings into policy and practice

Changes at the policy, clinician and patient levels are needed to ensure that all patients receive best practice evidence-based care. This will need to be supported by implementation research to evaluate the impact of any interventions. At the policy level a starting point would be the development of national clinical guidelines, establishing clear referral pathways, either directly from the general practitioner or after initial investigations, and including telehealth as appropriate.

The cornerstone of management for patients with pancreatic cancer is oversight by a highly skilled multidisciplinary team. Currently MDTs are recognised by Cancer Australia as providing optimal quality care, with increasing access a key element of the Cancer Service Networks National Program.[180] They are well supported by clinicians, particularly in the public sector.[172] MDTs are unregulated but resources (including web-based on-line tools)[311] are available to facilitate their

establishment and functioning.[186] Improving access to MDTs will facilitate an integrated team approach and help to support collaborative standardised care. In addition to the somewhat ad hoc state of MDTs, the physical size of Australia makes accessing MDT care challenging for patients who live in rural or remote areas. Improved access to telehealth technology for patients who are unable or unwilling to travel, or for rural practitioners, will enable patients and practitioners to effectively participate in multidisciplinary care planning and increase referral pathways. There is evidence to support the use of telehealth to deliver better health outcomes in regional and remote communities, with savings for the governments and support from patients and clinicians, but its use needs to be expanded.[259, 262, 312]

Hospital and surgeon case-volumes have previously been shown to influence the outcomes of patients undergoing pancreatic tumour resection. Our research did not find an effect of hospital volume, possibly because some centralisation has already occurred,[192] but we did find an effect of surgeon volume (Appendix H). Changes need to be implemented by policy makers, hospital boards and potentially the College of Surgeons to ensure that hepatobiliary surgeons are performing a sufficiently high number of these pancreatic surgeries to optimise patient outcomes. Our data suggest that surgeons should perform a minimum of four pancreatic cancer resections annually, but our sample size was too small to be confident that this is the ideal number. The Cancer Institute NSW has recently released a quality improvement statement indicating that hospital case load should be 6 or more pancreatic surgeries per year for optimal care but they did not specify the number per surgeon.[313] Evidence suggests that there should be ongoing national monitoring of the association between hospital/surgeon volume and patient outcomes.

While we did not formally analyse associations between palliative care referral and patient outcomes, our Delphi process highlighted the importance of palliative care involvement, given the poor survival outcomes of patients with pancreatic cancer. Early or increased palliative care involvement for patients was associated with improved survival for patients with advanced cancer.[164] Among patients with advanced pancreatic cancer, early referral reduced the use of chemotherapy within 14 days of death and reduced hospital admissions within 30 days of death.[163] Palliative Care Australia has set standards for practice and their service provision document outlines methods and resources to increase access to palliative care.[314] This is particularly critical for this vulnerable patient group.

Our data support the need for significant changes in practice. One way of supporting this change would be to implement a system whereby compliance with a series of quality indicators, such as those developed through our Delphi process, is continuously measured. Providing hospitals and

individual clinicians with reports which compare their processes and outcomes with that of others would enable them to identify where their practice differs from the norm and/or fails to adhere to accepted guidelines. The results of any policy or practice changes would be evident through this continuous benchmarking approach.

8.5. CONCLUSION

People diagnosed with pancreatic cancer suffer the worst five-year survival observed for any cancer. Resection of the primary tumour currently provides the greatest potential for cure. Increasing the proportion of patients who undergo surgical resection and ensuring that this occurs in a high case-volume setting may lead to population-level gains in survival. In addition, access to other cancer-directed therapies in both the adjuvant and palliative settings may lead to further improvements in both survival and quality of life.

There is considerable investment in identifying new strategies for diagnosis and treatment of pancreatic cancer. However, immediate improvements to patient outcomes could be made by implementing policies and procedures that enable all patients, irrespective of their sociodemographic characteristics, to be managed by high-performing multidisciplinary teams, ensuring accurate staging and receipt of optimal curative and supportive treatment modalities. This will also enable full realisation of benefits expected to accrue from the development of new treatments over the coming decades.

Chapter 9: References and Appendices

9.1. REFERENCES

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9.2. APPENDIX A

9.2.1. Pancreatic Cancer Patterns-of-Care Study Group

This group of clinicians collaborated with the patterns-of-care study team to facilitate data collection throughout New South Wales and Queensland.

Pancreatic Cancer Patterns-of-Care Study Group

Rick Abraham, FRACP, ICON Cancer Care; Ehtesham A Abdi, FRACP, Griffith University, Tweed Cancer Care Centre; Mark N. Appleyard, MD, Royal Brisbane and Women's Hospital; Gregory D. Barclay, FAChPM, University of Wollongong, Illawarra Shoalhaven Local Health District; Geoffrey F. Beadle, FRACP, Royal Brisbane and Women's Hospital, QIMR Berghofer Medical Research Institute; Lourens Bester, MD, University of Notre Dame, St Vincent's Hospital; Kate Blackler, RN, Cancer Council NSW; Antonino Bonaventura, FRACP, Calvary Mater Hospital, Newcastle; Fabio R. Brecciaroli, FAChPM, ANZSPM, Palliative Care QLD; Karen P. Briscoe, FRACP, North Coast Cancer Institute, NSW; Susan Brown, BA, QIMR Berghofer Medical Research Institute; Matthew E. Burge, FRACP, Royal Brisbane and Women's Hospital; Bryan H. Burmeister, MD, Princess Alexandra Hospital, University of Queensland; Leighna K. Carmichael, SM, Cancer Council NSW; David R.H. Christie, FRANZCR, Bond University, Genesiscare Tugun; Richard Chye, FAChPM, South East Sydney LHD & St Vincent's Network, University of New South Wales; Philip R. Clingan, FRACP, University of Wollongong, Illawarra Shoalhaven Local Health District; Aniko Cooper, BAppSc, Townsville Hospital; Tracie Corish, RN, QIMR Berghofer Medical Research Institute; Paul S. Craft, FRACP, The Canberra Hospital, Australian National University; Michelle Cronk, FRACP, Sunshine Coast Hospital and Health Service; Mark J. Deuble, FAChPM, Metro South Palliative Care Service, Brisbane; Benedict M. Devereaux, FRACP, University of Queensland; Paul Eliadis, FRACP Bond University; Jonathan Fawcett, DPhil, Princess Alexandra Hospital, University of Queensland; Robert J. Finch, FRACS, Royal Brisbane and Women's Hospital; Jonathan S. Gani, MD, University of Newcastle; David Goldstein, FRACP, Prince of Wales Hospital; Peter S. Grimison, PhD, Chris O'Brien Lifehouse, Sydney; Alexander D. Guminski, PhD, University of Sydney, Royal North Shore Hospital; Howard P. Gurney, FRACP, University of Sydney, Westmead Hospital; Christine L. Hill, BNP, QIMR Berghofer Medical Research Institute; Luke F. Hourigan, FRACP, Princess Alexandra Hospital, Greenslopes Private Hospital; George Hruby, FRANZCR, University of Sydney, Chris O'Brien Lifehouse; Warren L. Joubert, FRACP, Princess Alexandra Hospital, Greenslopes Private Hospital; Andrew B. Kneebone, FRANZCR, Northern Sydney Cancer Centre, University of Sydney; Stephen V. Lynch, FRACS, Princess Alexandra Hospital, University of Queensland;

Karen A. Martin, BHA, QIMR Berghofer Medical Research Institute; Gavin M. Marx, FRACP, University of Sydney, Sydney Adventist Hospital; Neil D. Merrett, FRACS, University of Western Sydney; Andrea D. McMurtrie, BN, QIMR Berghofer Medical Research Institute; Robyn Nagel, FRACP, University of Queensland; Weng L. Ng, PhD, Liverpool Hospital, Ingham Health Research Institute, Liverpool; Nicholas A. O'Rourke, FRACS, Royal Brisbane and Women's Hospital, University of Queensland; Nick Pavlakis, PhD, Royal North Shore Hospital, Sydney University; Leigh Rutherford, FRACS, Gold Coast University Hospital; Joseph J. Rutovitz, FRACP, Sydney Adventist Hospital, Northern Haematology and Oncology Group; Sabe Sabesan, FRACP, Townsville Cancer Centre, Townsville Hospital; Jaswinder S. Samra, DPhil, University of Sydney, Royal North Shore Hospital; Charbel Sandroussi, FRACS, Royal Prince Alfred Hospital, University of Sydney; Eva Segelov, PhD, St Vincent's Clinical School and Hospital; Thomas P. Shakespeare, FRANZCR , University of New South Wales; Geane S. Sharman, RN, Cancer Council NSW; Abdul Rahim Mohd Tahir, FRANZCR, North Coast Cancer Institute, NSW; Stephen R. Thompson, PhD, Prince of Wales Hospital, University of New South Wales; Shinn Tung Yeung, FRACS, Princess Alexandra Hospital, Greenslopes Hospital; Desmond Yip, FRACP, The Canberra Hospital, Australian National University.

9.3. APPENDIX B

9.3.1. Pancreatic cancer clinical working group

This group of clinicians from throughout Australia participated in the Delphi process to develop pancreatic cancer quality indicators.

Pancreatic cancer clinical working group:

Meera Agar, Flinders University & Braeside Hospital; Luisa Algie, The Princess Alexandra Hospital; Fabio Brecciaroli, Caloundra Hospital; Ann Bullen, The Royal Brisbane and Women's Hospital; Matthew Burge, The Royal Brisbane and Women's Hospital; Bryan H. Burmeister, University of Queensland and Princess Alexandra Hospital; Susan Caird, Gold Coast University Hospital & Griffith University; Donald Cameron, The Townsville Hospital; Philip Chan, University of Queensland & The Royal Brisbane and Women's Hospital; Lorraine Chantrill, Campbelltown Hospital & Garvan Institute; David Christie, Bond University & Genesiscare; Yu Jo Chua, The Canberra Hospital; Peter H. Cosman, University of Western Sydney ; John Croese, The Prince Charles Hospital; Michelle Cronk, Nambour General Hospital; Mark Deuble, Princess Alexandra Hospital; Melissa Eastgate, The Royal Brisbane and Women's Hospital; David Fletcher, University of Western Australia; Jon Gani, John Hunter Hospital; David Goldstein, Prince of Wales Hospital; Peter Grimison, Chris O'Brien Lifehouse; Saurabh Gupta, The Wesley Hospital & Princess Alexandra Hospital; George Hruby, University of Sydney & Chris O'Brien Lifehouse; Michael Jefford, Peter MacCallum Cancer Centre; Stephen V. Lynch, Mater Private Hospital & Princess Alexandra Hospital; Neil Merrett, Bankstown Hospital & University of Western Sydney; Jennifer Powell, The Royal Brisbane and Women's Hospital; David Pryor, Princess Alexandra Hospital; Spiro Raftopoulos, Sir Charles Gairdner Hospital; Jaswinder S. Samra, Royal North Shore Hospital & Macquarie University Hospital; Kellee Slater, Greenslopes Hospital & Princess Alexandra Hospital; Nigel Spry, Sir Charles Gairdner Hospital; Guy Van Hazel, University of Western Australia; Jane Whelan, Princess Alexandra Hospital; A. Peter Wysocki, Logan Hospital & Griffith University.

9.4. APPENDIX C

9.4.1. Patterns-of-care studies

Table 9-1: Patterns-of-care studies for patients diagnosed with pancreatic cancer, sorted by region and publication date

Reference	Sample	Data source	N	Aims/outcomes	Strengths	Limitations
United States						
Wolfson, 2015[123]	All PC aged 22 – 65 1998-2008	Los Angeles Cancer Registry	2,317	Comparing barriers to presentation at NCICCC and survival outcomes (v. not)	Clear methods. Standardised comprehensive data collection.	Minimal treatment data. Only used patients < 65years of age. No comorbidity adjustment.
Vijayvergiia, 2015[198]	Metastatic PC 2000-2010	Fox chase centre, PA	579	Comparing POC for patients < 65 years with those 65+ years		Single centre cohort. Retrospective chart review.
Abraham, 2013[10]	All PC 1994-2008	California Cancer Registry	20,312	Investigate socio-demographic variations in resectability, surgery and chemotherapy receipt.	Large population-based sample. Clear, concise methods and completed relevant sensitivity analyses.	Administrative data may cause under-reporting. Unable to adjust for performance status or comorbidities. Only first-line treatment data. No residential location or hospital volume analyses. Excluded patients with unknown surgery, chemotherapy or stage.
Oberstein, 2013[210]	Distant disease Stage IV PC, ≥ 65 years old 1998-2005	SEER, Medicare	3,094	Gemcitabine use for metastatic disease	Population-based. Adjusted for some patient factors.	SEER only covers ~ 20% of population during these years. 22% excluded due to death within 30 days of diagnosis. No performance status recorded. No patterns of use for other chemotherapy agents.
DaCosta, 2013[196]	PC in managed care 2001-2010	Private database	5,262	Costs, treatment patterns	Matched to 15786 controls = large sample size.	Selection-bias, private administrative data. Not population-based.
Singal, 2012[211]	Non-metastatic PC, 1998–2008,	9 States of United States, SEER registry	16,282	Comparing racial differences and survival.	Large sample size.	SEER only 26% of United States population, over represents minority groups therefore not true population. Lots of missing information including performance status, comorbidities and chemotherapy treatment details.
Seyedin, 2012[11]	Non- metastatic PC 1998-2002	SEER data	5,908	Investigate the impact of SES on resection rates	Large sample size.	SES calculated using only income as a measure. Low income group only 3.6% of sample.

Reference	Sample	Data source	N	Aims/outcomes	Strengths	Limitations
Gong, 2011[33]	All PC, San Francisco 1995-1999	SEER, California Cancer Centre	1,954	Population-based survival	Comprehensive data, thorough follow-up.	Small sample size. Majority was administrative data only. 42% of initial treatment patterns unknown.
Davilla, 2009[212]	Older than 65 years with surgical resection for PC 1992-2002	SEER - Medicare data	1,383	Surgery and adjuvant therapy patterns of care.	All patients had histological diagnosis. All records had linked medicare records so treatments should be recorded.	Identified using administrative data and coding records. No resection margin status or performance status. Small sample - excluded a lot of patients (eg missing hospital data and 30-day post-surgery death) Administrative data so under-reporting may occur (8% not covered).
Shavers, 2009[213]	All PC 1998	SEER and POC/QOC project	697	Racial/ethnic POC	Stratified groups. Had details of treatment refusal.	Only a sample of patients included from strata (more African Americans and Hispancis). No adjustment for facility or type of treatment centre. Old data.
Cress 2008[89]	All PC 1994-2000	California Cancer Registry	10,612	Survival by socio-demographic and treatment characteristics	Population-based. Large sample size.	Only basic demographics and tumour characteristics through chart review, data linkage for the rest and may be under-represented, no completion records. No performance status.
Bilimoria, 2007[13]	All PC 1985-2003	NCDB	301,033	Treatment trends (1985 – 1994 vs. 1995 – 2003)	Large sample size. Examines trends over time and also receipt of treatment by hospital type.	Unable to adjust for specific comorbidities or performance status. May have selection bias from registry and facilities of NCDB - only captures ~75% of population. Administrative data, no medical record review – may cause under-reporting.
Eloubeidi, 2006[195]	All PC 1996-2000	Alabama Cancer Registry	2,230	Survival prognostic factors.		11% incomplete registry data. 8% did not have adenocarcinoma.
Wasif, 2006[315]	Non-metastatic PC	NCDB	10,674	Investigate survival by distance travelled to treatment	Large sample size. Adjusted for comorbidities. Used propensity scoring to remove some treatment receipt bias.	Did not adjust for performance status - poorer status less likely to travel. Not truly population-based. NCDB only captures 70% of patients.
Krzyzanowska, 2003[214]	Locally advanced PC 1991-1996	SEER and Medicare	1,696	Treatment patterns for patients with locally advanced disease.	Pathologically confirmed pancreatic cancer. Propensity scoring used to assess effectiveness of treatment to alleviate selection bias.	Data linkage retrospective data. SEER data covers only ¬ 14% population. Medicare ¬95% population. Linkage has 94% match rate. Admin data = No performance status, limited health service data.

Reference	Sample	Data source	N	Aims/outcomes	Strengths	Limitations
Sener, 1999[215]	All PC 1985-1995	NCDB	100,313	Trends in stage, patterns and outcomes	Data collection was standardised. Large sample.	Survey completion Only patients that presented to NCDB hospitals – 60% of population.
Janes, 1996[197]	All PC 1983-1985 and 1990	Survey to institutions	16,942	Time trend for methods of diagnosis, staging, treatment and outcome	Large sample size	Retrospective descriptive data. Voluntary completion of surveys. Unreliable completion of survey data.
Wade, 1996[199]	Surgical resection PC 1989-1994	Dept. of Defence Hospitals	698	Treatment of pancreatic cancer and Whipples	Standardised records.	Includes all pancreatic cancers, and all types of surgical procedure. Old data. Low level statistics, no patient factor adjustments.
Canada						
Kagedan, 2016[216]	All PC Ontario, Canada 2005-2010	Cancer registry with data linkage	6,296	Investigate factors influencing the receipt of surgery	Large geographical area. Comprehensive surgical pathology reports.	Retrospective administrative data. No performance status. Incomplete staging information. Excluded patients dying within 6 months surgery for adjuvant treatment analyses.
Europe and Scandinavia						
Soreide, J 2016[194]	Surgical resection PC Stavanger, Norway 1986-2012	Registry Pancreatic surgery	219	Indications, outcomes of surgery over time	Complete patient population for hospital.	Small sample size. Only includes data from 1 hospital. All types of pancreatic surgery (eg trauma, IPMN etc)
Haj Mohammad, 2016[131]	Metastatic PC 2007-2011	Netherlands Cancer Registry	5,385	Volume of chemotherapy treatment facility with survival.	Population-based. Varying methods of categorising treatment facility.	May have selection bias – fitter patients presenting to higher volume centres. No performance status recorded which may be better indicator of survival.
Jooste, 2016[217]	All PC 2009-2011	2 Cancer Registry areas of France	554	Wait times from presentation to treatment and survival	Complete population-based. Accurate, reliable standardised data from registries.	Waiting times unknown for many patients.
Bernards, 2015[221]	Metastatic PC 1993-2010	South Netherlands Registry	3,099	Trends in chemotherapy and survival	Population-based	No performance status recorded – surrogate factor for chemotherapy and survival.
Sharp, 2009[12]	All PC 1994-2003	Ireland Cancer Registry Data	3,173	Patterns of care. Shows treatment trends with gemcitabine licensed in Ireland in 1998.	Includes all patients, truly population-based. Propensity score matching for survival and treatment receipt removed some bias.	Unknown how data was collected –registry notified and does mention chart review in discussion but not in methods. A large number of unknown stage (37%) No performance status or comorbidities recorded.

Reference	Sample	Data source	N	Aims/outcomes	Strengths	Limitations
David, M 2009[62]	All PC Burgundy, France 1976-2005	Digestive Cancer Registry Burgundy	2,986	Patterns of care and survival over time.	Provided a description of patterns of care over a 30 year period.	Limited methods description. Administrative data with no quality control. Only one area of France – not full population. Included neuro-endocrine tumours.
Bramhall, 1995[193]	All PC West Midlands 1957-1986	West Midlands Health Region	13,560	Patterns of care and survival over time	Large sample size with all pancreatic adenocarcinomas registered.	Not histologically confirmed (~ 40%) – could include other incorrect diagnoses. Incomplete retrospective data.
Australia						
Queensland Health, 2015[192]	All PC 2009-2011	Queensland Cancer Registry	664	Queensland oncology population based report pancreatic surgery	Population-based. All private and public inpatient records. Linked to cancer registry.	Coded and administrative data. No staging details. Included small intestine and biliary tract cancer.
Jefford, 2010,[18] Speer, 2012[107]	All PC 2002-2003	Victoria Cancer Registry, clinical survey	765	Patterns of care	Population-based.	Small sample size. ¬17% missing data. Measurement bias of survey. Limited staging details. Only descriptive statistics reported. Selection bias due to lack of information for the very ill patients.
Luke, 2009[316]	All PC 1997-2006	South Australian Cancer Registry,	4,166	Socio-demographic determinants of survival	Non adenocarcinomas were analysed separately. Population-based.	No treatment details or performance status, unable to adjust survival estimates.

PC: Pancreatic cancer; NCICCC: National Cancer Institute Cancer Care Centre; NCDB: National Cancer Database; SEER: Surveillance, Epidemiology and End Results program; POC: Patterns of care; QOC: quality of care IPMN: Intraductal papillary mucinous neoplasm; SES: Socio-economic status

9.5. APPENDIX D

9.5.1. Case Report Form

This form was based on a previous patterns-of-care study CRF[18] and went through a series of modifications.

Some issues were found with the data collection form; for example:

- Q11 staging required careful completion. Q11b was completed following all investigations prior to any treatment and the TNM staging was completed following all pathology (including surgery). The placement of Q11b preceding Q11a might have enhanced the flow of the data collection.
- Comorbidities were not coded according to severity and would have been more easily computed to a Charlson comorbidity index score if they had been collected and coded with the scoring method/reporting considered a priori.
- Initial treatment intent was difficult to establish with consistency, particularly for those patients receiving neoadjuvant treatment and locally advanced disease.
- A definition of hepatobiliary surgeon posed some queries as there were no formal qualifications required for this classification at the time of the study.
- No details of who attended the MDT were collected therefore it was unknown if the MDTs were formal or informal.

Pancreatic Cancer Patterns of Care Survey

QPCS / POC ID

TRACKING LOG FORM

HOSPITAL CODE WHERE FORM COMMENCED:

SURVEY FORM:

- ☐ Complete, form finalised
- ☐ Incomplete ---------> *Additional Sites to be visited*

Tick when complete

- ☐ ☐
- ☐ ☐
- ☐ ☐
- ☐ Form finalised

CXT FORM:

☐ N/A

- ☐ Complete, form finalised
- ☐ Incomplete ---------> *Additional Sites to be visited*

Tick when complete

- ☐ ☐
- ☐ ☐
- ☐ ☐
- Form finalised ☐

RXT FORM:

☐ N/A

- ☐ Complete, form finalised
- ☐ Incomplete ---------> *Additional Sites to be visited*

Tick when complete

- ☐ ☐
- ☐ ☐
- ☐ ☐
- Form finalised ☐

☐ **SURVEY FORM ONLY, NO SUBSEQUENT PRESENTATION FORMS COMPLETED**

☐ **CHART NOT FOUND**

Date Chart Commenced ☐☐ / ☐☐ / ☐☐

Date Chart Completed ☐☐ / ☐☐ / ☐☐ **Completed By**

Pancreatic Cancer Patterns of Care Survey

QPCS / POC ID

SECTION 1 : INITIAL PRESENTATION, INVESTIGATIONS AND STAGING

1. Date of 1st Diagnosis based on imaging:

1a. Date of histological/cytological diagnosis: N/A

2a. What was the final diagnosis?

5- ☐ Primary pancreatic cancer, *complete this review form (if NOS or exocrine malignant tumour type)*

1, 1a, 2a, 3 ☐ Ampullary cancer

☐ IPMN

☐ Cancer of other organ → ☐ bile duct/cholangiocarcinoma ☐ duodenum ☐ stomach ☐ other_____

complete questio ☐ Metastatic pancreatic cancer, *name primary site* _____

☐ Acute pancreatitis

☐ Chronic pancreatitis

☐ Other, please specify_____

☐ unknown

2b. Which specialist was the patient initially referred to?

- ☐ Gastroenterologist
- ☐ General Surgeon
- ☐ Specialist HPB Surgeon
- ☐ Upper GI Surgeon
- ☐ Radiation Oncologist
- ☐ Medical Oncologist
- ☐ Interventional Radiologist
- ☐ Palliative Care Physician
- ☐ Other, please specify _____
- ☐ Not stated

2c. What was the date of the first Palliative Care consultation?

NS N/A

2c.1. What was the date of first referral to palliative care outreach?

NS N/A

2c.2. Were there letters on file from palliative care services or GPs?

GP or PC	Date on letter

2d. Where did the patient see the first specialist?

- ☐ Public hospital
- ☐ Private hospital
- ☐ Private specialist rooms (in or not in hospital setting)

Hospital Code ☐

3. Was histology performed? *(please record for ALL cancers)*

N ☐ Y ☐ →*specify type* ☐ Biopsy ☐ Resection

SPECIFY SITES:
- ☐ primary tumour
- ☐ metastases
  - ☐ lymph nodes
  - ☐ liver
  - ☐ peritoneal
  - ☐ chest
  - ☐ other, please specify_____
  - ☐ not stated

3b. Was histology diagnostic?

N ☐ Y ☐

4. Was cytology performed? *(please record for ALL cancers)*

N ☐ Y ☐ ----→ *specify type* ☐ EUS guided FNA ☐ External U/S ☐ CT FNA ☐ ERCP brushings ☐ Not stated

SPECIFY SITES:
- ☐ primary tumour
- ☐ metastases
  - ☐ lymph nodes
  - ☐ liver
  - ☐ peritoneal
  - ☐ chest
  - ☐ other, please specify_____
  - ☐ not stated

4b. Was cytology diagnostic?

N ☐ Y ☐

5. What was the histological / cytological diagnosis?

EXOCRINE PANCREAS

☐ Malignant ------→ *specify type*

- ☐ Ductal adenocarcinoma , NOS
- ☐ Mucinous noncystic carcinoma
- ☐ Signet ring cell carcinoma
- ☐ Adenosquamous carcinoma
- ☐ Undifferentiated (anaplastic) carcinoma
- ☐ Undifferentiated carcinoma with osteoclast-like giant cells
- ☐ Mixed ductal-endocrine carcinoma
- ☐ Serous cystadenocarcinoma
- ☐ Mucinous cystadenocarcinoma, *specify type*
  - ☐ Invasive
  - ☐ Non-invasive
- ☐ Intraductal papillary-mucinous carcinoma, *specify type*
  - ☐ Invasive
  - ☐ Non-invasive
- ☐ Acinar cell carcinoma, *specify type*
  - ☐ Acinar cell cystadenocarcinoma
  - ☐ Mixed acinar-endocrine carcinoma
- ☐ Pancreatoblastoma
- ☐ Solid-pseudopapillary carcinoma
- ☐ not stated

☐ Benign → *specify type*

- ☐ benign, NOS
- ☐ mature teratoma
- ☐ cystadenoma, *specify type*
  - ☐ serous
  - ☐ mucinous
- ☐ Intraductal papillary-mucinous adenoma, *specify type*
  - ☐ branch duct
  - ☐ main duct

☐ Borderline → *specify type*

- ☐ Mucinous cystic neoplasm with moderate dysplasia
- ☐ Intraductal papillary-mucinous neoplasm with moderate dysplasia
- ☐ Solid-pseudopapillary neoplasm

ENDOCRINE PANCREAS

☐ Well-differentiated tumour →*specify type*

- ☐ Functioning, *specify type*
  - ☐ Insulin-producting (insuloma)
  - ☐ Glucagon-producting (glucagonoma)
  - ☐ Somatostatin-producing (somatostatinoma)
  - ☐ Gastrin-producing (gastrinoma)
  - ☐ VIP – producing (VIPoma)
- ☐ Non-functioning, *specify type*
  - ☐ Microadenoma (<0.5cm)
  - ☐ others

☐ Well-differentiated carcinoma →*specify type*

- ☐ Functioning, *specify type*
  - ☐ Insulin-producting (insuloma)
  - ☐ Glucagon-producting (glucagonoma)
  - ☐ Somatostatin-producing (somatostatinoma)
  - ☐ Gastrin-producing (gastrinoma)
  - ☐ VIP – producing (VIPoma)
  - ☐ Serotonin producing with carcinoid syndrome
  - ☐ ACTH producting with Cushing syndrome
- ☐ Non-functioning

☐ Poorly-differentiated endocrine carcinoma-small cell carcinoma

OTHER

☐ Lymphoma ☐ Other (please specify) _____

☐ Not stated

☐ No diagnostic histology / cytology performed

6. What was the site of the tumour? *(tick multiple sites if overlapping)*

- ☐ Uncinate process
- ☐ Head
- ☐ Neck
- ☐ Body
- ☐ Tail
- ☐ Ampulla of Vater
- ☐ Common bile duct (cholangiocarcinoma)
- ☐ Not stated

7. What was the indication that led to diagnosis?

☐ Incidental finding → *condition being Ix?*

☐ Clinical investigation for possible symptoms of pancreatic cancer

8. What were the patient's symptoms at the time of diagnosis?

- ☐ Asymptomatic
- ☐ Jaundice
- ☐ Back pain
- ☐ Abdominal pain
- ☐ Vomiting and/or nausea
- ☐ Altered bowel habit
- ☐ Weight loss
- ☐ Anorexia
- ☐ Fatigue, lethargy, tiredness
- ☐ Ascites
- ☐ Cholangitis
- ☐ Gastric outlet obstruction
- ☐ Acute pancreatitis
- ☐ Glucose intolerance
- ☐ Other, please specify _____
- ☐ Not stated

9. What diagnostic investigations were performed prior to treatment?

Test	Date 1st done	1st Ordered by	
		GP	Hosp/spec
CA19.9		☐	☐
Xray – plain abdo		☐	☐
Xray – plain chest		☐	☐
Endoscopy		☐	☐
Colonoscopy		☐	☐
US – abdo		☐	☐
CT – plain abdo		☐	☐
CT scan – pancreas protocol		☐	☐
CT – IV cholangio		☐	☐
MRI		☐	☐
MRCP		☐	☐
ERCP – Diagnostic		☐	☐
EUS (No FNA)		☐	☐
EUS guided FNA		☐	☐
PET		☐	☐
Angiography		☐	☐
Laparoscopy		☐	☐
Laparotomy		☐	☐
Core Bx/CT FNA cytology		☐	☐
Other, specify		☐	☐

10. What was the patient's ECOG performance status at time of diagnosis?

- ☐ 0 = fully active
- ☐ 1 = limited activity
- ☐ 2 = in bed < 50% of the day
- ☐ 3 = in bed > 50% of the day
- ☐ 4 = bed bound
- ☐ Not stated

☐ ECOG written in chart

11a. What was the TNM stage of this tumour?

- ☐ **TX** primary tumour cannot be assessed
- ☐ **TO** no evidence of primary tumour
- ☐ **Tis** carcinoma in situ
- ☐ **T1** tumour limited to pancreas, 2cm or less in greatest dimension
- ☐ **T2** tumour limited to pancreas, more than 2cm in greatest dimension
- ☐ **T3** tumour extends beyond the pancreas but without involvement of the celiac trunk or superior mesenteric artery
- ☐ **T4** tumour involves the celiac axis or superior mesenteric artery (unresectable primary tumour)

- ☐ **NX** regional lymph nodes cannot be assessed
- ☐ **NO** no regional lymph node metastases
- ☐ **N1** regional lymph node metastases

- ☐ **MX** distant metastases cannot be assessed
- ☐ **MO** no distant metastases
- ☐ **M1** distant metastases

11a.2. Was there perineural invasion?

- ☐ Yes
- ☐ No
- ☐ Not stated

☐ TNM score not stated / cannot be imputed from the records

11b. Was the tumour considered to be: *(based on imaging or exploratory lap.)*

☐ resectable -→ ☐ confined to pancreas
☐ locally advanced

☐ non resectable -→ ☐ metastatic
☐ locally advanced

12. Were any comorbidities present prior to diagnosis? N NS Y ---→ *specify all that apply*

- ☐ Diabetes: NIDDM → date of dx ___ / ___ / _____ and/or IDDM→ date of dx ___ / ___ / _____
- ☐ Ischemic Heart Disease → date of dx ___ / ___ / _____
- ☐ CVA → date of dx ___ / ___ / _____
- ☐ COAD, lung disease → date of dx ___ / ___ / _____
- ☐ Renal/Kidney disease → date of dx ___ / ___ / _____
- ☐ HIV→ date of dx ___ / ___ / _____
- ☐ Depression → date of dx ___ / ___ / _____
- ☐ Other cancer: site, _____→ date of dx ___ / ___ / _____ site, _____→ date of dx ___ / ___ / _____
- ☐ Hypertension
- ☐ Obesity
- ☐ Dementia, confusion
- ☐ GORD (reflux) → date of dx ___ / ___ / _____
- ☐ Other, please specify_____
- ☐ Not stated

12b. Was there a past history of pancreatic pathology?

N Y →

- ☐ Chronic pancreatitis
- ☐ Acute pancreatitis
- ☐ IPMN
- ☐ Other

If yes, when was it first diagnosed? ___ / ___ / _____

12c. What was the patient's smoking status at the time of diagnosis?

Never smoker ☐ Past smoker ☐ Current smoker ☐ Unknown ☐

12d. Was there a family history of cancer? N Y

If yes list family member and site of cancer,

SECTION 2 : TREATMENT PHASE

13. What was the initial treatment intent for this patient?

- ☐ curative
- ☐ palliative
- ☐ not stated
- ☐ patient refused treatment ⟶ ☐ Surgery ☐ Chemotherapy/radiotherapy

14. Was curative surgery for resection attempted?

N ------⟶ *please specify reason:*

Go to Qu 18

- ☐ Peritoneal metastases
- ☐ Liver metastases
- ☐ Locally advanced disease
- ☐ Advanced age
- ☐ Comorbidities
- ☐ Patient declined surgery
- ☐ Deceased prior to scheduled surgery
- ☐ Other, please specify_____
- ☐ Not stated

Y ⟶ *please specify type:*

- ☐ Whipple procedure --⟶
  - ☐ pylorus preserved
  - ☐ feeding jejunostomy
  - ☐ surgery aborted
- ☐ Total pancreatectomy -⟶
  - ☐ pylorus preserved
  - ☐ feeding jejunostomy
  - ☐ surgery aborted
- ☐ Distal pancreatectomy -⟶
  - ☐ surgery completed
  - ☐ surgery aborted
- ☐ Not stated

------⟶ date of surgery ☐☐☐☐☐☐☐☐ NS

Place of surgery: *(hospital code)* ☐☐☐

Surgeon: *(surgeon code)* ☐☐☐

Hepatobiliary surgeon N Y NS

14b. What was the date of the most recent staging?

☐☐☐☐☐☐☐☐

14b.1. Did the most recent staging occur in the same hospital as the surgery?

N Y NS

15. Did surgical intent change intra-operatively?

N | Y ----→ *please specify reason*

- ☐ Metastases present
  Biopsied ☐ Yes ☐ No ☐ Not stated
- ☐ Locally advanced disease -----> *specify extent*
  - ☐ Portal Vein invasion
  - ☐ Arterial invasion
- ☐ Intra-operative complication
- ☐ Other, please specify_____
- ☐ Not stated

16. What margins were achieved with surgery? ☐ Write in clearance margin if available

- ☐ clear < 1mm
- ☐ clear 1 to less than 2mm
- ☐ clear 2 to 5mm
- ☐ clear >5mm
- ☐ involved margins
- ☐ clear margins, distance not stated
- ☐ not stated

17. Was frozen section done during surgery?

N | NS | Y

18. Did the patient undergo bypass surgery?

N | NS | Y ----→ *date of surgery* ☐☐ ☐☐ ☐☐☐☐

----→ *please specify type*

- ☐ Cholecystojejunostomy
- ☐ Choledochojejunostomy (Rouex en Y)
- ☐ Gastrojejunostomy
- ☐ Hepaticojejunostomy
- ☐ Other, please specify _____
- ☐ Not stated

19a. Which of the following complications arose (within 30 days) from surgical resection?

Tick all that apply

- ☐ anastamotic leak
- ☐ persisting jaundice
- ☐ wound infection
- ☐ intra-abdominal sepsis
- ☐ gastric outlet obstruction
- ☐ haemorrhage
- ☐ delayed gastric emptying
- ☐ fistula
- ☐ pulmonary infection
- ☐ not applicable
- ☐ none
- ☐ other, *please specify*_____
- ☐ not stated

19b. Which of the following complications arose (within 30 days) from bypass surgery?

Tick all that apply

- ☐ anastamotic leak
- ☐ persisting jaundice
- ☐ wound infection
- ☐ intra-abdominal sepsis
- ☐ gastric outlet obstruction
- ☐ haemorrhage
- ☐ delayed gastric emptying
- ☐ fistula
- ☐ pulmonary infection
- ☐ not applicable
- ☐ none
- ☐ other, *please specify*_____
- ☐ not stated

19c. If the patient underwent curative OR palliative surgery, record the PRE-operative

WBC (x10^9/L) _____ Date_____ Albumin Level (g/L) _____ Date_____

20. Did the patient undergo biliary stenting?

N ⟶ *go to Q 22* NS Y ⟶ *please specify*

STENT 1
Date of insertion
__ / __ / ____

Reason for insertion
- ☐ Primary insertion
- ☐ blocked/obstructed
- ☐ routine replacement
- ☐ conversion to metal
- ☐ infection
- ☐ not stated

Method of insertion
- ☐ Endoscopic Management
  - ☐ Endoscopic Stent
    - ☐ plastic
    - ☐ metal
    - ☐ not stated
- ☐ Interventional radiology
  - ☐ Percutaneous Stent
    - ☐ plastic
    - ☐ metal
    - ☐ not stated
- ☐ Not stated

STENT 2
Date of insertion
__ / __ / ____

Reason for insertion
- ☐ Primary insertion
- ☐ blocked/obstructed
- ☐ routine replacement
- ☐ conversion to metal
- ☐ infection
- ☐ not stated

Method of insertion
- ☐ Endoscopic Management
  - ☐ Endoscopic Stent
    - ☐ plastic
    - ☐ metal
    - ☐ not stated
- ☐ Interventional radiology
  - ☐ Percutaneous Stent
    - ☐ plastic
    - ☐ metal
    - ☐ not stated
- ☐ Not stated

STENT 3
Date of insertion
__ / __ / ____

Reason for insertion
- ☐ Primary insertion
- ☐ blocked/obstructed
- ☐ routine replacement
- ☐ conversion to metal
- ☐ infection
- ☐ not stated

Method of insertion
- ☐ Endoscopic Management
  - ☐ Endoscopic Stent
    - ☐ plastic
    - ☐ metal
    - ☐ not stated
- ☐ Interventional radiology
  - ☐ Percutaneous Stent
    - ☐ plastic
    - ☐ metal
    - ☐ not stated
- ☐ Not stated

21. Which of the following complications arose (within 30 days) from stent insertion?

STENT 1
- ☐ pancreatitis
- ☐ cholangitis
- ☐ persisting jaundice
- ☐ bile leak
- ☐ haemorrhage
- ☐ other, please specify

  _____
- ☐ none
- ☐ not stated

STENT 2
- ☐ pancreatitis
- ☐ cholangitis
- ☐ persisting jaundice
- ☐ bile leak
- ☐ haemorrhage
- ☐ other, please specify

  _____
- ☐ none
- ☐ not stated

STENT 3
- ☐ pancreatitis
- ☐ cholangitis
- ☐ persisting jaundice
- ☐ bile leak
- ☐ haemorrhage
- ☐ other, please specify

  _____
- ☐ none
- ☐ not stated

22. Did the patient have a duodenal obstruction?

N ------→ *go to Qu 24* NS Y ------→ *please specify*

Episode 1

Reason for obstruction:

- ☐ tumour growth
- ☐ radiation complication
- ☐ not stated

Treatment received:

- ☐ No treatment
- ☐ Duodenal stent inserted
  Date of insertion
  ___ / ___ / _____
- ☐ Bypass --> *specify type*
  - ☐ laparoscopic
  - ☐ surgery
  - ☐ not stated

  Date of bypass
  ___ / ___ / _____
- ☐ Not stated

Episode 2

Reason for obstruction:

- ☐ tumour growth
- ☐ radiation complication
- ☐ not stated

Treatment received:

- ☐ No treatment
- ☐ Duodenal stent inserted
  Date of insertion
  ___ / ___ / _____
- ☐ Bypass --> *specify type*
  - ☐ laparoscopic
  - ☐ surgery
  - ☐ not stated

  Date of bypass
  ___ / ___ / _____
- ☐ Not stated

Episode 3

Reason for obstruction:

- ☐ tumour growth
- ☐ radiation complication
- ☐ not stated

Treatment received:

- ☐ No treatment
- ☐ Duodenal stent inserted
  Date of insertion
  ___ / ___ / _____
- ☐ Bypass --> *specify type*
  - ☐ laparoscopic
  - ☐ surgery
  - ☐ not stated

  Date of bypass
  ___ / ___ / _____
- ☐ Not stated

23. Were there any complications following duodenal stent insertion?

Episode 1

N NS Y --→ *describe*

_____

_____

Episode 2

N NS Y --→ *describe*

_____

_____

Episode 3

N NS Y --→ *describe*

_____

_____

24. Was the patient enrolled in a clinical trial for ca pancreas?

☐ no, no mention of a trial in the chart

☐ no, trial considered but patient not eligible

☐ no, trial discussed but declined by patient (*name of trial)*_____

☐ yes (*name of trial)*_____

25. Did the patient see a MEDICAL oncologist?

NS

N ------→ *please specify reason*

- ☐ Not indicated
- ☐ Patient declined
- ☐ Too unwell
- ☐ Deceased prior to review
- ☐ Other, *please specify* _____

Y ------→ what date did the patient first see the med onc? ☐☐ / ☐☐ / ☐☐

was the patient offered adjuvant/curative CXT? Y →*complete box below* N NS

- ☐ Treated with adjuvant/curative chemotherapy, *please complete CXT form*
- ☐ Treated with combined adjuvant/curative chemo/radiotherapy, *please complete CXT and RXT forms*
- ☐ Patient declined treatment
- ☐ Too unwell to proceed with planned CXT
- ☐ Deceased prior to planned CXT commencing
- ☐ Other, *please specify* _____

------→ was the patient offered palliative CXT? Y ------→*complete box below* N NS

- ☐ Treated with palliative chemotherapy, *please complete CXT form*
- ☐ Treated with combined palliative chemo/radiotherapy, *please complete CXT and RXT forms*
- ☐ Patient declined treatment
- ☐ Too unwell to proceed with planned CXT
- ☐ Deceased prior to planned CXT commencing
- ☐ Other, *please specify* _____

26. Did the patient see a RADIATION oncologist?

NS

N ------→ *please specify reason*

- ☐ Not indicated
- ☐ Patient declined
- ☐ Too unwell
- ☐ Deceased prior to review
- ☐ Other, *please specify* _____

Y ------→ what date did the patient first see the RAD onc? ☐☐ / ☐☐ / ☐☐

was the patient offered adjuvant/curative RXT? Y →*complete box below* N NS

- ☐ Treated with adjuvant/curative radiotherapy, *please complete RXT form*
- ☐ Treated with combined adjuvant/curative chemo/radiotherapy, *please complete CXT and RXT forms*
- ☐ Patient declined treatment
- ☐ Too unwell to proceed with planned RXT
- ☐ Deceased prior to planned RXT commencing
- ☐ Other, *please specify* _____

------→ was the patient offered palliative RXT? Y ------→*complete box below* N NS

- ☐ Treated with palliative radiotherapy, *please complete RXT form*
- ☐ Treated with combined palliative chemo/radiotherapy, *please complete CXT and RXT forms*
- ☐ Patient declined treatment
- ☐ Too unwell to proceed with planned RXT
- ☐ Deceased prior to planned RXT commencing
- ☐ Other, *please specify* _____

27a. Was this patient presented at a multidisciplinary team meeting?

N ⟶ *go to Qu 28* ⟵ NS Y ⟶ *go to Qu 27b*

27b. Who referred this patient to the MDT meeting?

- ☐ Gastroenterologist
- ☐ General Surgeon
- ☐ Specialist HPB surgeon
- ☐ Radiation Oncologist
- ☐ Medical Oncologist
- ☐ Interventional Radiologist
- ☐ Palliative Care Physician
- ☐ Other, please specify _____
- ☐ Not stated

27c. When was the patient first presented to the MDT meeting?

___ /___/ _____ *other dates if multiple presentations* ___ /___/ _____ and ___ /___/ _____ or NS

The following questions relate to review by allied health professionals

28a. Was the patient referred to a dietitian?

N NS Y → ☐ Seen as an inpatient / outpatient

☐ Community referral

28b. Did the patient have evidence of a navigator / care plan?

N NS Y → ☐ Seen as an inpatient / outpatient

☐ Community referral

28c. Was the patient referred to a psychologist or counsellor?

N NS Y → ☐ Seen as an inpatient / outpatient

☐ Community referral

28c. Was the patient referred to a social worker?

N NS Y → ☐ Seen as an inpatient / outpatient

☐ Community referral

28d. Was there evidence that this patient was prescribed pancreatic enzymes (CREON)?

Y N

28e. Did the patient have one or more celiac plexus blocks for pain management?

Y N

If yes, please record dates of blocks

1. ___ /___/ ____
2. ___ /___/ ____
3. ___ /___/ ____
4. ___ /___/ ____
5. ___ /___/ ____

29a. What was the patient's status 12 months after diagnosis?

Alive ☐ Deceased ☐ Not stated ☐

If ALIVE: What was the disease status?

- ☐ No sign of recurrence
- ☐ Local disease
- ☐ Locally advanced disease
- ☐ Metastatic disease
- ☐ Both local and distant disease
- ☐ Disease status unknown

Where was the patient living?

- ☐ Independent at home
- ☐ Living in hospice
- ☐ Inpatient in hospital
- ☐ Living in Palliative Care Facility
- ☐ Other, please specify _____
- ☐ Not stated

29b. What was the patient's status 6 months after diagnosis?

Alive ☐ Deceased ☐ Not stated ☐

If ALIVE: What was the disease status?

- ☐ No sign of recurrence
- ☐ Local disease
- ☐ Locally advanced disease
- ☐ Metastatic disease
- ☐ Both local and distant disease
- ☐ Disease status unknown

Where was the patient living?

- ☐ Independent at home
- ☐ Living in hospice
- ☐ Inpatient in hospital
- ☐ Living in Palliative Care Facility
- ☐ Other, please specify _____
- ☐ Not stated

29c. If DECEASED: What was the date of death? ☐☐ ☐☐ ☐☐☐☐

What was the primary cause of death?

- ☐ Complications of surgery for cancer
- ☐ Complications of other treatment for cancer
- ☐ Cancer
- ☐ Other please specify _____
- ☐ Not stated

What was the place of death?

- ☐ Home
- ☐ Hospice
- ☐ Inpatient in hospital
- ☐ Other please specify_____
- ☐ Not stated

SECTION 3 : RECURRENCE / PROGRESSION (after curative surgery)

30. Did the patient suffer a recurrence / progression after surgery?

N NS N/A

Y → Date of recurrence / progression diagnosis (dd/mm/yyyy)

31.a. What treatment did the patient receive for recurrence?

- ☐ None
- ☐ Surgical Resection
- ☐ Palliative radiotherapy
- ☐ Palliative chemotherapy
- ☐ Palliative chemotherapy and radiotherapy
- ☐ Palliative bypass surgery
- ☐ Stent placement----> *specify type* ☐ Biliary ☐ Duodenal
- ☐ Pain management ----> *specify type*
  - ☐ splanchnic nerve block ☐ EUS ☐ CT
  - ☐ coeliac plexus nerve block ☐ EUS ☐ CT
  - ☐ splanchnectomy
  - ☐ opiod analgesia
  - ☐ non-opioid analgesia
    - ☐ tramadol
    - ☐ anti-inflammatory
    - ☐ other, please specify _____
- ☐ Anti-epileptics
- ☐ Therapeutic ascetic tap
- ☐ Blood Transfusion
- ☐ Treatment of cachexia ☐ TPN ☐ drug therapy, name _____
- ☐ Other please specify _____
- ☐ Not stated

SECTION 4: INPATIENT PRESENTATIONS

Presentation Number

Admission unrelated to pancreatic cancer ☐
(Don't complete form)

Primary reason for admission:

1. Date of admission: (dd/mm/yyyy)

2. Date of discharge: (dd/mm/yyyy)

3. Hospital code:

4. Who referred this patient for admission?

- ☐ Patient self – referral
- ☐ GP
- ☐ Transfer from another hospital, *hospital code*
- ☐ Gastroenterologist
- ☐ General Surgeon
- ☐ Specialist HPB surgeon
- ☐ Radiation Oncologist
- ☐ Medical Oncologist
- ☐ Interventional Radiologist
- ☐ Palliative Care Physician
- ☐ Other, please specify _____
- ☐ Not stated

5. Which Specialist primarily managed the patient during the admission?

- ☐ Gastroenterologist
- ☐ General Surgeon
- ☐ Specialist HPB surgeon
- ☐ Radiation Oncologist
- ☐ Medical Oncologist
- ☐ Interventional Radiologist
- ☐ Palliative Care Physician
- ☐ Other, please specify _____
- ☐ Not stated

6. Which other Specialist / Allied Health Therapist was consulted during the admission?

- ☐ Gastroenterologist
- ☐ General Surgeon
- ☐ Specialist HPB surgeon
- ☐ Radiation Oncologist
- ☐ Medical Oncologist
- ☐ Interventional Radiologist
- ☐ Palliative Care Physician
- ☐ Pain Management Team
- ☐ Endocrinologist
- ☐ Cardiologist
- ☐ Psychiatrist
- ☐ Dietician
- ☐ Physiotherapist
- ☐ Other, please specify _____
- ☐ None

7a. What was the PRIMARY reason for this admission? *(tick one)*

- ☐ Surgical resection *(curative pancreatectomy)*
- ☐ Other surgery _____
- ☐ Complications of surgery
- ☐ Biliary Stent insertion
- ☐ Duodenal Obstruction
- ☐ Pain management
- ☐ Jaundice
- ☐ Ascites
- ☐ Chemotherapy
- ☐ Complications of chemotherapy
- ☐ Further staging work up
- ☐ Recurrence
- ☐ Palliative admission
- ☐ Terminal care
- ☐ Other, please specify _____
- ☐ Not stated

8a. What symptoms were present at the time of admission? *(tick all that apply)*

- ☐ Asymptomatic
- ☐ Jaundice
- ☐ Back pain
- ☐ Abdominal pain
- ☐ Vomiting and/or nausea
- ☐ Altered bowel habits
- ☐ Weight loss
- ☐ Anorexia
- ☐ Cachexia
- ☐ Ascites
- ☐ Cholangitis
- ☐ Gastric outlet obstruction
- ☐ Acute pancreatitis
- ☐ Glucose intolerance
- ☐ Fatigue, lethargy, tiredness
- ☐ Other, please specify _____

9. What was the patient's ECOG performance status at admission?

- ☐ 0 = fully active
- ☐ 1 = limited activity
- ☐ 2 = in bed < 50% of the day
- ☐ 3 = in bed > 50% of the day
- ☐ 4 = bed bound
- ☐ Not stated

ECOG written in chart ☐

10. What investigations were undertaken during this admission? *(tick all that apply, including those not able to be completed due to complications)*

- ☐ LFTs
- ☐ CEA
- ☐ Xray – plain abdominal
- ☐ Xray- plain chest
- ☐ endoscopy
- ☐ US – transabdominal
- ☐ CT – was a pancreas specific protocol followed? *N* *Y*
- ☐ CT – intravenous cholangiogram
- ☐ PTC - percutaneous transhepatic cholangiogram
- ☐ MRI
- ☐ MRCP
- ☐ ERCP – Diagnostic
- ☐ ERCP – Biliary stent placed
- ☐ EUS
- ☐ PET
- ☐ Angiography
- ☐ Laparoscopy
- ☐ Laparotomy
- ☐ Core biopsy/CT guided /EUS FNA cytology/histology of PANCREAS
- ☐ Core biopsy/CT guided/EUS FNA cytology/histology of METASTASES
- ☐ Other, please specify _____
- ☐ None

11. Did the patient receive treatment during this admission?

N ----→ ☐ none recommended

☐ Patient declined

Y ----→ (*tick all that apply)*

- ☐ Surgical Resection
- ☐ Palliative radiotherapy
- ☐ Palliative chemotherapy
- ☐ Palliative chemotherapy and radiotherapy
- ☐ Palliative bypass surgery
- ☐ Stent placement (successful) ----> *specify type* ☐ Biliary ☐ Duodenal
- ☐ Attempted (failed) stent placement ----> *specify type* ☐ Biliary ☐ Duodenal
- ☐ Pain management ----> *specify type*
  - ☐ splanchnic nerve block ☐ EUS ☐ CT
  - ☐ coeliac plexus nerve block ☐ EUS ☐ CT
  - ☐ splanchnectomy
  - ☐ opioid analgesia
  - ☐ non-opioid analgesia
    - ☐ tramadol
    - ☐ anti-inflammatory
    - ☐ other, please specify _____
- ☐ Anti-epileptics
- ☐ Therapeutic ascetic tap
- ☐ Blood Transfusion
- ☐ Treatment of cachexia ☐ TPN ☐ drug therapy, name _____
- ☐ Treatment of nausea ----> Specify drug names_____
- ☐ Other please specify _____
- ☐ Not stated

12. What happened at the end of this admission?

☐ Deceased

☐ Discharged home

☐ Transferred to another hospital for treatment , *hospital code* ☐☐☐☐☐

☐ Other, *please specify*_____

☐ Not stated

13. How many days during this admission were spent in HDU / ICU? ☐☐☐

Comments:

Pancreatic Cancer Patterns of Care Survey

QPCS / POC ID

CHEMOTHERAPY FORM

Course Number: ☐ First line ☐ OR Second line ☐ Third line ☐

Concurrent radiotherapy: Yes ☐ No ☐

Timing: Neoadjuvant ☐ Adjuvant ☐ Palliative ☐

Response to treatment: Complete response ☐ Partial response ☐ Stable disease ☐ Disease progression ☐ Don't know ☐

Was the planned course completed? Yes ☐ No ☐ Don't know ☐

If no, reason for cessation:
- ☐ Complications (specify) _____
- ☐ Patient declined further treatment
- ☐ Disease progression
- ☐ Other (specify) _____

Baseline WBC ($x10^9$/L) _____ Date _____

Baseline Albumin Level (g/L) _____ Date _____

Cycle #	PLANNED DOSING PATTERN	PLANNED STARTING DRUG NAME #1	PLANNED DOSE mg	PLANNED STARTING DRUG NAME #2	PLANNED DOSE mg

only complete shaded section if starting dose is different to planned dose

Cycle #	Date	Drug Name	Dose mg	Bolus or infusion
				B ☐ I ☐
				B ☐ I ☐
				B ☐ I ☐
				B ☐ I ☐
				B ☐ I ☐
				B ☐ I ☐
				B ☐ I ☐
				B ☐ I ☐

Pancreatic Cancer Patterns of Care Survey

QPCS ID

SUPPLEMENTARY RADIOTHERAPY QUESTIONNAIRE

RADIOTHERAPY COURSE NO: ☐ **SITE/S TREATED** ☐

1. Who referred the patient to the Radiation Oncologist for radiotherapy?

- ☐ General Practitioner
- ☐ Gastroenterologist
- ☐ General Surgeon
- ☐ Specialist HPB surgeon
- ☐ Radiation Oncologist
- ☐ Medical Oncologist
- ☐ Interventional Radiologist
- ☐ Palliative Care Physician
- ☐ Other, please specify _____
- ☐ Not stated

2. What was the initial treatment intent of this course of radiotherapy?

- ☐ Palliative
- ☐ Curative
  - ☐ Curative, definitive treatment
  - ☐ Pre-operative, downstaging
  - ☐ Post-operative radiotherapy ⟶ *what was the indication:*
    - ☐ Routine adjuvant therapy
    - ☐ Positive margins
    - ☐ Microscopic residual disease
    - ☐ Macroscopic residual disease
    - ☐ Node positive
    - ☐ High risk primary, *please specify*
      - ☐ Close margins
      - ☐ Lymphovascular space invasion
      - ☐ High grade tumour
    - ☐ Other, please specify_____
    - ☐ Not stated
- ☐ Not stated

3. Did the treatment intent change during this course of radiotherapy?

N ☐ NS ☐ Y ☐ ⟶ *please specify reason:* _____

4. Did the patient receive concurrent chemotherapy?

N ☐ NS ☐ Y ☐

Pancreatic Cancer Patterns of Care Survey

QPCS ID

5. a) What was the total dose prescribed?

- ☐ 45 Gy / 25#
- ☐ 50.4 Gy / 28#
- ☐ 54 Gy / 30#
- ☐ Other, *please specify* _____
- ☐ Not stated

b) What dose was actually delivered?

- ☐ 45 Gy / 25#
- ☐ 50.4 Gy / 28#
- ☐ 54 Gy / 30#
- ☐ Other, *please specify* _____
- ☐ Not stated

6. Please record the following dates for this course of radiotherapy:

☐☐ ☐☐ ☐☐☐☐ *Date RXT commenced: Dd/mm/yyyy*

☐☐ ☐☐ ☐☐☐☐ *Date RXT completed: Dd/mm/yyyy*

7. Did the patient require treatment for radiation toxicity?

N | NS | Y ⟶ *please specify type of toxicity and RTOG grade*

- ☐ Nausea Grade _____
- ☐ Vomiting Grade _____
- ☐ Diarrhea Grade _____
- ☐ Stomatitis Grade _____
- ☐ Other, please specify _____
- ☐ Not stated

8. What was the patient's response to this course of radiotherapy?

- ☐ Complete response
- ☐ Partial response
- ☐ Stable disease
- ☐ Disease progression
- ☐ Not stated

9.6. APPENDIX E

9.6.1. Supplementary tables for Chapter 6 (Survival and determinants of surgery)

Table 9-2: Association betweeeween patients, tumour and health service factors and attempted resection(adjusted odds ratio) in patients with non-metastatic disease (N= 768)

	All patients with non-metastatic disease			Confined to pancreas disease			Locally advanced disease (LAD)		
Exposure Variable	Total	Resection n (%)	AOR (95% CI)[a]	Total	Resection n (%)	AOR (95% CI)[b]	Total	Resection n (%)	AOR (95% CI)[b]
Remoteness of residence (ARIA)									
Major City	542	258 (48)	1	156	99 (63)	1	386	159 (41)	1
Inner Regional	163	74 (45)	0.85 (0.55, 1.32)	44	30 (68)	0.92 (0.29, 2.92)	119	44 (37)	0.81 (0.50, 1.30)
Remote	76	31 (41)	0.57 (0.30, 1.07)	23	17 (74)	1.09 (0.15, 7.68)	53	14 (26)	0.48 (0.24, 0.99)
Overall p value, p trend			0.20, 0.08			0.99, 0.99			0.12, 0.05
Socioeconomic status of residence									
Most disadvantaged (1)	156	73 (47)	1	46	32 (70)	1	110	41 (37)	1
2	171	80 (47)	0.81 (0.47, 1.40)	48	31 (65)	0.78 (0.18, 3.42)	123	49 (40)	0.82 (0.45, 1.49)
3	158	68 (43)	0.77 (0.43, 1.35)	45	30 (67)	0.39 (0.08, 1.89)	113	38 (34)	0.76 (0.41, 1.41)
4	160	77 (48)	0.79 (0.45, 1.39)	53	34 (64)	0.59 (0.14, 2.47)	107	43 (40)	0.86 (0.46, 1.60)
Least disadvantaged (5)	136	65 (48)	1.04 (0.58, 1.86)	31	19 (61)	2.50 (0.48, 12.92)	105	46 (44)	1.01 (0.54, 1.88)
Overall p value, p trend			0.76, 0.95			0.34, 0.58			0.87, 0.91
Sex									
Female	364	143 (39)	1	102	60 (59)	1	262	83 (32)	1
Male	422	222 (53)	1.30 (0.91, 1.85)	123	88 (72)	1.33 (0.52, 3.44)	299	134 (45)	1.33 (0.90, 1.96)
Overall p value			0.15			0.55			0.15
Age-group[c]									
< 60	141	103 (73)	1	43	43 (100)		98	60 (61)	1
60 - 69	218	135 (62)	0.59 (0.36, 0.98)	55	49 (89)	Omitted[f]	163	86 (53)	0.67 (0.40, 1.14)
70 - 79	223	107 (48)	0.37 (0.22, 0.61)	62	49 (79)		161	58 (36)	0.42 (0.24, 0.71)
80 +	204	20 (10)	0.04 (0.02, 0.07)	65	7 (11)		139	13 (9)	0.09 (0.04, 0.18)
Overall p value, p trend			< 0.001, < 0.001						< 0.001, < 0.001

	All patients with non-metastatic disease			Confined to pancreas disease			Locally advanced disease (LAD)		
Exposure Variable	Total	Resection n (%)	AOR (95% CI)[a]	Total	Resection n (%)	AOR (95% CI)[b]	Total	Resection n (%)	AOR (95% CI)[b]
Charlson score[c]									
0	340	184 (54)	1	88	73 (83)	1	252	111 (44)	1
1	243	105 (43)	0.76 (0.52, 1.10)	66	43 (65)	0.54 (0.22, 1.31)	177	62 (35)	0.81 (0.54, 1.24)
2	199	74 (37)	0.57 (0.38, 0.85)	69	31 (45)	0.29 (0.12, 0.70)	130	43 (33)	0.74 (0.46, 1.17)
Overall p value, p trend			0.02, 0.005			0.02, 0.01			0.38, 0.17
Performance status on presentation									
Fully active	260	183 (70)	1[d]	100	91 (91)	1[d]	160	92 (58)	1[d]
Not fully active	420	134 (32)	0.29 (0.19, 0.42)	55	33 (60)	0.05 (0.1, 0.15)	185	73 (39)	0.40 (0.26, 0.61)
Overall p value			< 0.001			< 0.001			< 0.001
Clinical staging	768	365 (46)							
Confined disease			1	225	148 (66)				
Locally advanced			0.21 (0.14, 0.33)				561	217 (39)	
Overall p value			< 0.001						
Site tumour									
Head/neck	647	298 (46)	1	184	114 (62)	1	463	184 (40)	1
Body	40	14 (35)	0.47 (0.21, 1.04)	11	8 (73)	1.98 (0.23, 17.24)	29	6 (21)	0.33 (0.12, 0.86)
Tail	43	33 (77)	3.64 (1.50, 8.84)	16	16 (100)	Omitted	27	17 (63)	2.35 (0.95, 5.80)
Multiple/other	33	13 (39)	0.53 (0.22, 1.27)	8	7 (88)	0.66 (0.04, 9.82)	25	6 (24)	0.42 (0.15, 1.15)
Overall p value			0.003			0.79			0.01
Majority admissions									
Public	535	226 (42)	1	125	79 (63)	1	410	147 (36)	1
Private	249	139 (56)	1.25 (0.85, 1.83)	99	69 (70)	1.65 (0.62, 4.43)	150	70 (47)	1.29 (0.84, 1.99)
Overall p value			0.26			0.32			0.24
Attended MDT									
No / Not stated	518	239 (46)	1	163	107 (66)	1	355	132 (37)	1
Yes	268	126 (47)	0.67 (0.46, 0.97)	62	41 (66)	0.29 (0.09, 0.93)	206	85 (41)	0.74 (0.50, 1.11)
Overall p value			0.04			0.04			0.14

	All patients with non-metastatic disease			Confined to pancreas disease			Locally advanced disease (LAD)		
Exposure Variable	Total	Resection n (%)	AOR (95% CI)[a]	Total	Resection n (%)	AOR (95% CI)[b]	Total	Resection n (%)	AOR (95% CI)[b]
First specialist seen									
HPB	145	87 (60)	1	58	48 (83)	1	87	39 (45)	1
Gastroenterologist	235	123 (52)	1.17 (0.70, 1.93)	62	44 (71)	0.96 (0.26, 3.54)	173	79 (46)	1.34 (0.76, 2.36)
General Surgeon	292	118 (40)	0.79 (0.48, 1.29)	70	41 (59)	0.29 (0.08, 1.07)	222	77 (35)	0.99 (0.57, 1.71)
Other	114	37 (32)	0.68 (0.36, 1.28)	35	15 (43)	0.32 (0.06, 1.63)	79	22 (28)	0.81 (0.39, 1.68)
Overall p value			0.18			0.15			0.38
Seen at major hospital (≥ 6 resections, yr^{-1})									
No	579	235 (41)	1	147	84 (57)	1	432	151 (35)	1
Yes	207	130 (63)	2.11 (1.40, 3.19)	78	64 (82)	4.46 (1.42, 13.94)	129	66 (51)	1.89 (1.20, 2.97)
Overall p value			< 0.001			0.01			0.01
Initial facility case-volume									
30 +	411	226 (55)	1	136	100 (74)	1	275	126 (46)	1
10 – 29	232	97 (42)	0.72 (0.48, 1.07)	62	36 (58)	0.61 (0.19, 1.96)	170	61 (36)	0.74 (0.48, 1.14)
< 10	132	42 (32)	0.66 (0.39, 1.10)	25	12 (48)	0.33 (0.07, 1.57)	107	30 (28)	0.67 (0.39, 1.16)
Overall p value, p trend			0.13, 0.05			0.32, 0.13			0.22,0.10

Notes: Adjustment variables: [a] age group (<60, 60-69, 70-79, 80+ years); performance status (0, 1, 2+, not stated); and clinical staging (confined to pancreas, locally advanced disease); [b] age group (<60, 60-69, 70-79, 80+ years); performance status (0, 1, 2+, not stated); [c] performance status; [d] age group, [e] not adjusted. [f] omitted as all reference category patients had attempted surgery. [g] includes uncinate process

Missing (not stated) data: Place of residence, n = 5; SES, n = 5; Charlson, n = 4; Performance status, n = 106; Initial facility volume, n =11; Majority of admissions, n = 2.

Place of residence groups defined by Accessibility/Remoteness Index of Australia (ARIA); Performance status defined by Eastern Cooperative Oncology Group (ECOG); SES Socio-Economic Status defined by Socio-Economic Indexes for Areas; First facility volume by the number of study participant initial presentations.

Table 9-3: Unadjusted associations between patient, tumour and health-service factors and (1) attempted resection (n = 786); (2) classification of disease resectability (n=561); (3) attempted resection for patients classified as resectable (n = 510)

	(1) Non-metastatic disease			(2) Locally advanced disease[a]			(3) Classified as resectable[a]		
		Attempted resection			Classified as resectable			Attempted resection	
Variable	Total	n (%)	Crude OR[b] (95% CI)	Total	n (%)	Crude OR[b] (95% CI)	Total	n (%)	Crude OR[b] (95% CI)
Patient / tumour factors									
Age at diagnosis, years									
< 60	141	103 (73)	1.00	98	62 (63)	1.00	105	103 (98)	1.00
60 - 69	218	135 (62)	0.60 (0.38, 0.95)	163	91 (56)	0.73 (0.44, 1.23)	146	135 (92)	0.24 (0.05, 1.10)
70 - 79	223	107 (48)	0.34 (0.22, 0.54)	161	76 (47)	0.52 (0.31, 0.87)	138	107 (78)	0.07 (0.02, 0.29)
≥ 80	204	20 (10)	0.04 (0.02, 0.07)	139	56 (40)	0.39 (0.23, 0.67)	121	20 (17)	0.00 (0.00, 0.02)
Overall p value, p trend			<0.001, <0.001			0.002, < 0.001			<0.001, <0.001
Sex									
Men	422	222 (53)	1.00	299	164 (55)	1.00	287	222 (77)	1.00
Women	364	143 (39)	0.58 (0.44, 0.77)	262	121 (46)	0.71 (0.51, 0.99)	223	143 (64)	0.52 (0.35, 0.77)
Overall p value			<0.001			0.04			0.001
Performance status									
Fully active	260	183 (70)	1.00	160	95 (59)	1.00	195	183 (94)	1.00
Not fully active	420	134 (32)	0.20 (0.14, 0.28)	325	156 (48)	0.63 (0.43, 0.93)	251	134 (53)	0.08 (0.04, 0.14)
Overall p value			<0.001			0.02			< 0.001
Charlson comorbidity index (score)									
Low (0)	340	184 (54)	1.00	252	126 (50)	1.00	214	184 (86)	1.00
Medium (1)	243	105 (43)	0.65 (0.46, 0.90)	177	91 (51)	1.06 (0.72, 1.55)	157	105 (67)	0.34 (0.20, 0.56)
High (≥ 2)	199	74 (37)	0.50 (0.35, 0.72)	130	66 (51)	1.03 (0.68, 1.57)	135	74 (55)	0.20 (0.12, 0.34)
Overall p value, p trend			< 0.001, < 0.001			0.96, 0.85			< 0.001, < 0.001
Place of residence									
Major city	542	258 (48)	1.00	386	206 (53)	1.00	362	258 (71)	1.00[d]
Inner Regional	163	74 (45)	0.92 (0.64, 1.30)	119	50 (50)	0.89 (0.59, 1.34)	104	74 (71)	0.99 (0.61, 1.61)
Outer regional / remote	76	31 (41)	0.76 (0.47, 1.23)	53	19 (36)	0.49 (0.27, 0.89)	42	31 (74)	1.14 (0.55, 2.34)
Overall p value, p trend			0.51, 0.26			0.06, 0.03			0.94, 0.80

	(1) Non-metastatic disease			(2) Locally advanced disease[a]			(3) Classified as resectable[a]		
		Attempted resection			Classified as resectable			Attempted resection	
Variable	Total	n (%)	Crude OR[b] (95% CI)	Total	n (%)	Crude OR[b] (95% CI)	Total	n (%)	Crude OR[b] (95% CI)
SES - quintiles									
Most disadvantaged	156	73 (47)	1.00	110	55 (50)	1.00	101	73 (72)	1.00
Second	171	80 (48)	1.00 (0.65, 1.54)	123	65 (53)	1.12 (0.67, 1.88)	113	80 (71)	0.93 (0.51, 1.69)
Third	158	68 (43)	0.86 (0.55, 1.34)	113	50 (44)	0.79 (0.47, 1.34)	95	68 (72)	0.97 (0.52, 1.80)
Fourth	160	77 (48)	1.05 (0.68, 1.64)	107	56 (52)	1.10 (0.64, 1.87)	109	77 (71)	0.92 (0.51, 1.68)
Least disadvantaged	136	65 (48)	1.04 (0.66, 1.65)	105	59 (56)	1.28 (0.75, 2.19)	90	65 (72)	1.00 (0.53, 1.88)
Overall p value, p trend			0.90, 0.81			0.48, 0.46			1.00, 0.98
Tumour site									
Head/neck/uncinate process	647	298 (46)	1.00	463	240 (52)	1.00	424	298 (70)	1.00
Body	40	14 (35)	0.63 (0.32, 1.23)	29	8 (28)	0.35 (0.15, 0.82)	19	14 (74)	1.18 (0.42, 3.36)
Tail	43	33 (77)	3.86 (1.87, 7.97)	27	21 (78)	3.25 (1.29, 8.20)	37	32 (89)	3.49 (1.21, 10.05)
Multiple/other	33	13 (39)	0.76 (0.37, 1.56)	25	8 (32)	0.44 (0.19, 1.03)	16	13 (81)	1.83 (0.51, 6.54)
Overall p value			< 0.001			0.001			0.11
Health Service Factors									
Evidence of MDT review									
No / not stated	518	239 (46)	1.00	355	193 (54)	1.00	356	239 (67)	1.00
Yes	268	126 (47)	1.04 (0.77, 1.39)	206	92 (45)	0.68 (0.48, 0.96)	154	126 (82)	2.20 (1.38, 3.51)
Overall p value			0.82			0.03			0.001
First facility case-volume[g]									
30 +	411	226 (55)	1.00	275	153 (56)	1.00	289	226 (78)	1.00
10 – 29	232	97 (42)	0.59 (0.42, 0.81)	170	84 (49)	0.78 (0.53, 1.14)	146	97 (66)	0.55 (0.35, 0.86)
< 10	132	42 (32)	0.38 (0.25, 0.58)	107	48 (45)	0.65 (0.41, 1.02)	73	42 (58)	0.38 (0.22, 0.65)
Overall p value, p trend			< 0.001, < 0.001			0.13, 0.05			< 0.001, < 0.001
Specialist first seen									
Hepatobiliary surgeon	235	87 (60)	1.00	87	44 (51)	1.00	102	87 (85)	1.00
Gastroenterologist	235	123 (52)	0.73 (0.48, 1.11)	173	97 (56)	1.25 (0.74, 2.09)	159	123 (66)	0.59 (0.30, 1.14)
General Surgeon	292	118 (40)	0.45 (0.30, 0.68)	222	108 (49)	0.93 (0.56, 1.52)	178	118 (66)	0.34 (0.18, 0.64)
Other	114	37 (32)	0.32 (0.19, 0.54)	79	36 (46)	0.82 (0.44, 1.51)	71	37 (52)	0.19 (0.09, 0.39)
Overall p value			< 0.001			0.36			< 0.001
Seen by hepato-biliary surgeon									
No / not stated	395	106 (27)	1.00	308	129 (42)	1.00	216	106 (49)	1.00
Yes	391	259 (66)	5.35 (3.94, 7.26)	253	156 (62)	2.23 (1.59, 3.13)	294	259 (88)	7.68 (4.93, 11.95)
Overall p value			< 0.001			< 0.001			< 0.001

	(1) Non-metastatic disease			(2) Locally advanced disease[a]			(3) Classified as resectable[a]		
		Attempted resection			Classified as resectable			Attempted resection	
Variable	Total	n (%)	Crude OR[b] (95% CI)	Total	n (%)	Crude OR[b] (95% CI)	Total	n (%)	Crude OR[b] (95% CI)
Pancreas protocol computerised tomography									
No / not stated	406	173 (43)	1.00	294	150 (51)	1.00	262	173 (66)	1.00
Yes	380	192 (51)	1.38 (1.04, 1.82)	267	135 (51)	0.98 (0.70, 1.37)	248	192 (77)	1.76 (1.19, 2.61)
Overall p value			0.03			0.91			0.005
Plain computerised tomography									
No / not stated	261	133 (51)	1.00	189	104 (55)	1.00	176	133 (76)	1.00
Yes	525	232 (44)	0.76 (0.57, 1.03)	372	181 (49)	0.77 (0.55, 1.10)	334	232 (69)	0.74 (0.49, 1.11)
Overall p value			0.07			0.15			0.15
Endoscopic ultrasound									
No / not stated	434	186 (43)	1.00	311	168 (54)	1.00	291	186 (64)	1.00
Yes	352	179 (51)	1.38 (1.04, 1.83)	250	117 (47)	0.75 (0.54, 1.05)	219	179 (82)	2.53 (1.66, 3.84)
Overall p value			0.03			0.09			<0.001
Laparoscopy									
No / not stated	648	252 (39)	1.00	455	201 (44)	1.00	394	252 (64)	1.00
Yes	138	113 (82)	7.10 (4.48, 11.26)	106	84 (79)	4.82 (2.91, 7.99)	116	113 (97)	21.22 (6.62, 68.03)
Overall p value			< 0.001			< 0.001			< 0.001
Endoscopic retrograde cholangiopancreatography									
No / not stated	399	190 (48)	1.00	276	134 (49)	1.00	257	190 (74)	1.00
Yes	387	175 (45)	0.91 (0.69, 1.20)	285	151 (53)	1.19 (0.86, 1.66)	253	175 (69)	0.79 (0.54, 1.16)
Overall p value			0.50			0.29			0.23
Magnetic resonance imaging /cholangiopancreatography									
No / not stated	642	285 (44)	1.00	462	236 (51)	1.00	416	285 (69)	1.00
Yes	144	80 (56)	1.57 (1.09, 2.25)	99	49 (49)	0.94 (0.61, 1.45)	94	80 (85)	2.63 (1.44, 4.81)
Overall p value			0.02			0.77			0.002

[a] Based on clinical staging including imaging or exploratory laparoscopy.

[b] Crude odds ratios (ORs,) estimated using logistic regression.

[g] Results from a mixed effects model with hospital as random intercept to adjust for hospital clustering.

Place of residence groups defined by Accessibility/Remoteness Index of Australia (ARIA); Performance status defined by Eastern Cooperative Oncology Group (ECOG); SES Socio-Economic Status defined by Socio-Economic Indexes for Areas; First facility volume by the number of study participant initial presentations.

Missing data: SES, n = 5; Place of residence, n = 5; Tumour site, n = 23; Performance status, n = 106; Charlson comorbidity index, n = 4; First inpatient facility volume, n = 11.

Table 9-4: Associations between patient, tumour and health-service factors and (1) place of residence and (2) age, for patients with non-metastatic disease on clinical staging.

	Place of residence, n (%) (n = 781)				Age in years, n (%) (n = 786)				
Exposure variable	Major city (n = 542)	Inner regional (n = 163)	Rural (n = 76)	P value[b]	< 60 (n = 141)	60 – 69 (n =218)	70 – 79 (n = 223)	≥ 80 (n = 204)	P value[b]
Patient / Tumour factors									
Age at diagnosis, years				0.44					
< 60	89 (16)	33 (20)	19 (25)						
60 - 69	161 (29)	40 (25)	17 (22)		Not applicable				
70 - 79	158 (29)	45 (28)	20 (26)						
≥ 80	139 (25)	45 (28)	20 (26)						
Sex				0.89					< 0.001
Men	292 (54)	85 (52)	42 (55)		85 (60)	139 (64)	110 (49)	88 (43)	
Women	85 (46)	78 (48)	34 (45)		56 (40)	79 (36)	113 (51)	116 (57)	
ECOG performance status									
0	173 (32)	56 (34)	27 (36)	0.41	67 (48)	95 (44)	64 (29)	34 (17)	< 0.001
1	159 (29)	57 (35)	24 (32)		52 (37)	73 (33)	73 (33)	42 (21)	
2+	131 (24)	30 (18)	19 (25)		12 (9)	21 (10)	49 (22)	98 (48)	
Not stated	79 (15)	20 (12)	6 (8)		10 (7)	29 (13)	37 (17)	30 (15)	
Charlson comorbidity index (score)									
Low (0)	244 (45)	63 (39)	30 (40)	0.61	82 (58)	92 (42)	98 (44)	68 (34)	0.002
Medium (1)	164 (30)	55 (34)	23 (31)		32 (23)	68 (31)	72 (32)	71 (35)	
High (≥ 2)	132 (24)	44 (27)	22 (29)		27 (19)	57 (26)	52 (23)	63 (31)	
Place of residence									0.50
Major city					89 (63)	157 (73)	157 (71)	139 (68)	
Inner Regional	Not applicable				33 (23)	40 (19)	45 (20)	45 (22)	
Rural					19 (13)	17 (8)	20 (9)	20 (10)	
Socioeconomic status				< 0.001					0.62
Most disadvantaged	82 (15)	41 (25)	33 (43)		27 (19)	32 (15)	51 (23)	46 (23)	
Second	84 (16)	72 (44)	15 (20)		34 (24)	44 (21)	50 (23)	43 (21)	
Third	110 (20)	30 (18)	18 (24)		31 (22)	49 (23)	38 (17)	40 (20)	
Fourth	133 (25)	17 (10)	10 (13)		30 (21)	47 (22)	46 (21)	37 (18)	
Least disadvantaged	133 (25)	3 (2)	0		19 (13)	42 (20)	37 (17)	38 (19)	

Exposure variable	Place of residence, n (%) (n = 781)				Age in years, n (%) (n = 786)				
	Major city (n = 542)	Inner regional (n = 163)	Rural (n = 76)	P value[b]	< 60 (n = 141)	60 – 69 (n =218)	70 – 79 (n = 223)	≥ 80 (n = 204)	P value[b]
Tumour site				0.47					0.85
Head/neck/uncinate process	452 (85)	135 (88)	57 (78)		115 (83)	182 (85)	180 (83)	170 (87)	
Body	27 (5)	7 (5)	6 (8)		8 (6)	9 (4)	14 (6)	9 (5)	
Tail	31 (6)	5 (3)	7 (10)		9 (7)	12 (6)	15 (7)	7 (4)	
Multiple/other	23 (4)	7 (5)	3 (4)		6 (4)	11 (5)	7 (3)	9 (5)	
Clinical Stage				0.85					0.46
Confined to the pancreas	158 (29)	44 (27)	23 (30)		43 (31)	55 (25)	62 (28)	65 (32)	
Locally advanced disease	389 (71)	119 (73)	53 (70)		98 (69)	163 (75)	161 (72)	139 (68)	
Health System Factors									
Evidence of MDT review				0.13					< 0.001
No / not stated	351 (65)	105 (64)	58 (76)		71 (50)	133 (61)	149 (67)	165 (81)	
Yes	191 (35)	58 (36)	18 (24)		70 (50)	85 (39)	74 (33)	39 (19)	
Specialist first seen				< 0.001					< 0.001
Hepatobiliary surgeon	121 (22)	22 (14)	2 (3)		24 (17)	60 (28)	42 (19)	19 (9)	
Gastroenterologist	174 (32)	38 (23)	21 (28)		52 (37)	56 (26)	73 (33)	54 (26)	
General Surgeon	170 (31)	86 (53)	33 (43)		52 (37)	77 (35)	78 (35)	85 (42)	
Other	77 (14)	17 (10)	20 (26)		13 (9)	25 (11)	30 (13)	46 (23)	
First inpatient facility volume				< 0.001					< 0.001
30 +	339 (63)	58 (36)	13 (17)		84 (60)	127 (58)	117 (52)	83 (41)	
10 – 29	139 (26)	54 (34)	36 (48)		35 (25)	68 (31)	67 (30)	62 (30)	
< 10	56 (10)	49 (30)	26 (35)		19 (13)	21 (10)	36 (16)	56 (27)	
Reviewed by hepato-biliary surgeon				0.009					< 0.001
No / not stated	262 (48)	80 (49)	51 (67)		54 (38)	86 (39)	101 (45)	154 (75)	
Yes	280 (52)	83 (51)	25 (33)		87 (62)	132 (61)	122 (55)	50 (25)	
Chemotherapy				0.32					< 0.001
No / not stated	259 (48)	83 (51)	43 (57)		36 (26)	56 (26)	119 (53)	176 (86)	
Yes	283 (52)	80 (49)	33 (43)		105 (74)	162 (74)	104 (47)	28 (14)	
Pancreas protocol computerised tomography				0.20					< 0.001
No / not stated	269 (50)	93 (57)	42 (55)		59 (42)	101 (46)	118 (53)	128 (63)	
Yes	273 (50)	70 (43)	34 (45)		82 (58)	117 (54)	105 (47)	76 (37)	

Exposure variable	Place of residence, n (%) (n = 781)				Age in years, n (%) (n = 786)				
	Major city (n = 542)	Inner regional (n = 163)	Rural (n = 76)	P value[b]	< 60 (n = 141)	60 – 69 (n =218)	70 – 79 (n = 223)	≥ 80 (n = 204)	P value[b]
Plain computerised tomography				0.01					0.22
No / not stated	196 (36)	44 (27)	17 (22)		50 (35)	82 (38)	64 (29)	65 (32)	
Yes	346 (64)	119 (73)	59 (78)		91 (65)	136 (62)	159 (71)	139 (68)	
Endoscopic ultrasound				< 0.001					< 0.001
No / not stated	273 (50)	104 (64)	55 (72)		61 (43)	110 (50)	113 (51)	150 (74)	
Yes	269 (50)	59 (36)	21 (28)		80 (57)	108 (50)	110 (49)	54 (26)	
Laparoscopy				0.11					< 0.001
No / not stated	439 (81)	135 (83)	69 (91)		107 (76)	174 (80)	168 (75)	199 (98)	
Yes	103 (19)	28 (17)	7 (9)		34 (24)	44 (20)	55 (25)	5 (2)	
Endoscopic retrograde cholangiopancreatography				0.02					0.69
No / not stated	269 (50)	79 (48)	50 (66)		76 (54)	114 (52)	111 (50)	98 (48)	
Yes	273 (50)	84 (52)	26 (34)		65 (46)	104 (48)	112 (50)	106 (52)	
Magnetic resonance imaging/cholangiopancreatography				0.93					<0.001
No / not stated	444 (82)	132 (81)	63 (83)		105 (74)	170 (78)	181 (81)	186 (91)	
Yes	98 (18)	31 (19)	13 (17)		36 (26)	48 (22)	42 (19)	18 (9)	

[a] Tumour status based on imaging or exploratory laparoscopy. [b] Chi-square test. [c] Missing data: SES, n = 5; Tumour site, n = 21; Charlson comorbidity index, n = 4; Clinical stage , n = 43, First facility volume, n = 11.

Table 9-5: Association between evidence of presentation at a multidisciplinary team meeting and survival, stratified by whether or not resection was attempted.

	Attempted resection			No attempted resection		
	n (%)	HR (95% CI)[a]	AHR (95% CI)[b]	n (%)	HR(95% CI)	AHR(95% CI)[b]
MDT[c]						
No	239 (65)	1.00	1.00	279 (66)	1.00	1.00
Yes	126 (35)	0.80 (0.63, 1.03)	0.77 (0.59, 1.00)	142 (34)	0.76 (0.62, 0.93)	0.80 (0.64, 1.00)

[a] HR = Hazard ratio; AHR = Adjusted HR; CI = Confidence Interval.

[b] Adjusted for performance status, age, place of residence and clinical stage of disease

[c] MDT= Review by multidisciplinary team

9.7. APPENDIX F

9.7.1. Introduction

This invited editorial has been published in Cancer Forum. The aim of this publication was to describe equity of access issues for patients with pancreatic cancer in Australia.

9.7.2. Contribution of candidate

Associate Professor Rachel Neale conceptualised, designed, wrote and submitted this invited editorial. My contribution included referencing (50%) and editing the publication (10%).

9.7.3. Manuscript

The following invited editorial was published in Cancer Forum, March 2016:

Patterns of care – improving equity of access to optimal care

Rachel E Neale, Elizabeth Burmeister. Cancer Forum; 40 (1).

Abstract

People diagnosed with pancreatic cancer suffer the worst five-year survival of any cancer. Resection of the primary tumour currently provides the only potential for cure. Increasing the proportion of patients who undergo surgical resection and ensuring that this occurs in a high-volume setting may lead to population-level survival gains. Access to chemotherapy in both adjuvant and palliative settings may lead to further improvements.

Worse survival has been reported for patients from lower socio-economic and rural areas than those who are wealthier and living in major cities. Management in higher-volume hospitals tends to be associated with higher survival. Differences in patient factors such as age, performance status and the presence of co-morbidities may partly explain the survival discrepancies; however, international and limited Australian data suggest that not all patients receive optimal treatment, and that variability in care may be related to socio-demographic factors.

There is considerable investment in identifying new strategies for diagnosis and treatment. However, immediate improvements could be made by implementing policies and procedures that enable all patients to be managed by high-performing multidisciplinary teams, ensuring receipt of optimal curative and supportive treatment modalities. This will also enable full realisation of benefits expected to accrue from the development of new treatments over the coming decades.

Introduction

Pancreatic cancer is the tenth most commonly occurring cancer in Australia, affecting over 2,700 people each year. It has the worst five-year survival of any cancer at less than five percent, so takes the lives of over 2,500 Australians annually and is the fourth-leading cause of cancer death in both men and women.[35] There has been little change in the mortality to incidence ratio since the early 1980s, in contrast with a number of other cancers. As a result it has been estimated that within the next decade it will become the second-leading cause of cancer death in the United States[40] and this is likely also to be the case in Australia.

The dismal prognosis in patients with pancreatic cancer is due firstly to the late stage at which most people are diagnosed. Consistent with international estimates,[317] almost 60% of pancreatic cancer patients in Australia are diagnosed with metastatic disease which precludes resection of the tumour.[293] A further 20-30% of patients have locally advanced disease and, although surgical techniques have improved, the vascular involvement is frequently too extensive to permit resection. The second reason for the poor survival has been the lack of efficacious systemic treatments. Until recently, administration of gemcitabine was considered the standard of care in both adjuvant and palliative settings, despite only small improvements in survival. The use of new regimens such as FOLFIRINOX and albumin-bound paclitaxel for treatment of inoperable pancreatic cancer, and increased investment in discovery of new therapies, may lead to further improvements in pancreatic cancer survival in the next decade.

Ensuring all patients receive optimal treatment will help to realise potential survival gains. However, international data suggests that patients from lower socioeconomic and rural areas may have worse survival than their counterparts from wealthier and metropolitan areas[89, 308] and similar trends for geographic location have been observed in Australia.[303, 304] While differences in patient factors such as age and the presence of co-morbidities may partly explain the survival discrepancies, it is likely that differential access to treatment also plays a role.

Increasing the proportion of patients who undergo resection of the primary tumour

Surgical resection of the primary tumour improves five-year survival from less than 5% to up to 20%,[157] but, consistent with international estimates, only 15% of patients in two states of Australia underwent resection between 2009 and 2011.[293] Population-level survival estimates would improve if this proportion could be increased. It has been estimated that increasing the proportion of patients diagnosed with stage one and two (i.e., operable) disease from 6% to 19%, with a concomitant decrease in the proportion of patients with metastatic disease, would double five-year survival.[317]

Earlier diagnosis might increase the proportion of patients diagnosed with operable disease. Some studies,[318, 319] although not all,[320] indicate that diagnostic delay is associated with later stage disease and poorer outcomes. However, a substantial component of the delay occurs as a result of the non-specific nature of symptoms which do not prompt early presentation to medical practitioners, and it is unlikely that this will be amenable to significant improvement. Implementation of screening programs has more potential to lead to a shift in the distribution of the stage of disease at diagnosis but considerable challenges remain. Population-wide screening is not feasible due to the relative rarity of pancreatic cancer. Indeed, modelling studies suggest that such an approach would reduce life expectancy due to false positive results and unnecessary surgery.[321] Screening is therefore currently restricted to people with genetic predisposition to pancreatic cancer and is only occurring within the context of research studies. Attempts to identify other subgroups of the population that have sufficiently high risk to make screening viable have so far proven unsuccessful.[322] Further, current screening relies on either computed tomography or magnetic resonance imaging; these are insufficiently accurate for identifying small tumours, may not be easily accessible and are expensive. Until these issues are resolved and screening becomes a feasible option it is doubtful that there will be any discernible increase in the proportion of patients diagnosed with early stage, operable disease.

A second approach to increasing the proportion of patients who undergo surgery is to ensure that this treatment option is offered to all patients with resectable tumours and acceptable performance status. International data show that there is currently inequitable access to surgical intervention, with patients who are Black, unmarried, have low education or socioeconomic status, and who come from rural rather than metropolitan areas being less likely to undergo resection of the primary tumour[10-13] This is most probably associated with the expertise of the facility at which patients are staged. Patients who are managed at high volume or accredited cancer centres have higher likelihood of undergoing surgery than those who are treated at lower volume centres, and there is evidence that centralisation of care can increase resection rates.[129] There is limited published Australian information about patient factors such as education which might influence access to surgical treatment, but our unpublished data suggests that remoteness of residential location is inversely associated with resection, and a Queensland report shows a slightly higher resection proportion in more affluent patients with cancers of the pancreas, biliary tract and small intestine combined.[192] Guidelines suggest that all patients without metastatic disease should be assessed for tumour resectability by a multidisciplinary team that includes a specialist hepatobiliary surgeon;[6] developing referral pathways or telehealth facilities that enable implementation of this guideline has the potential to increase the number of patients in Australia that are offered a resection of their tumour.

Surgical volume and mortality / survival

Pancreatic cancer surgery is challenging due to the anatomic location of the pancreas with its close proximity to large blood vessels into which the tumour has frequently invaded. The experience of the hospital at which patients are treated is therefore an important determinant of outcomes. A meta-analysis of 11 studies, most from the United States and none from Australia, found that patients treated in higher volume hospitals had lower post-operative mortality and longer overall survival.[114] The cut points for high and low volume varied markedly, however, so volume is likely to be a marker of expertise and multidisciplinary care but there is little evidence upon which to base recommendations about the minimum number of surgeries that should be performed. This is reflected in the guidelines which are inconsistent, with the NCCN recommending a minimum of 15 surgeries per year, the National Cancer Institute Guidelines recommending five and the British Society of Gastroenterology not specifying a particular number. There are no specific Australian guidelines. Between 2005 and 2008 in New South Wales pancreatic cancer surgery took place at 37 hospitals. Only six of these performed more than 6 pancreatic cancer surgeries annually, and 15 (41%) undertook fewer than two procedures each year.[209] Between 2002 and 2011 in Queensland 23 hospitals performed pancreaticoduodenectomies; by 2011 this number had dropped to 13,[192] indicating that centralisation of care has been occurring in some jurisdictions.

Adjuvant chemotherapy

There is a high risk of recurrence after resection of the primary pancreatic tumour, with median disease-free survival of less than one year.[143] Clinical practice guidelines therefore recommend adjuvant chemotherapy or chemo-radiotherapy,[6] although the type of therapy to be used is not specified, probably due to a lack of consensus about the interpretation of clinical trial data. As with surgery, international evidence suggests variable implementation of adjuvant therapy. A recent report from the Netherlands found that only about half of patients received adjuvant chemotherapy, but this was higher in patients who underwent their resection at a high-volume hospital.[323] Similarly, studies from the United States found that receipt of adjuvant therapy was higher among patients treated at high volume hospitals (vs low volume) and at academic rather than community hospitals[13] and in white rather than black patients.[10] In Australia chemotherapy with gemcitabine has been the standard of care, particularly since the publication of the CONKO-01 trial in 2007.[143] Presumably as a result of this key publication, use of adjuvant chemotherapy increased from 47% in Victorian patients diagnosed in 2002-2003 to 76% in patients from Queensland and New South Wales diagnosed almost a decade later. Patients who did not receive adjuvant treatment had worse performance status or a complicated post-operative course (unpublished data). This suggests that most Australian

patients who undergo surgery are now receiving appropriate multi-modality postoperative care in accordance with guidelines.

Chemotherapy in advanced pancreatic cancer

The majority of patients present with metastases or locally advanced inoperable disease. For these patients there have been limited curative treatment options and symptom control has been the primary aim of management. In 1997 a landmark study was published which showed that, although gemcitabine resulted in only a modest survival benefit over 5-flurouracil, it delivered substantial improvements in pain, performance status and weight.[149] It subsequently became the standard of care for first line treatment in patients with advanced disease. As with surgery and adjuvant chemotherapy, there is evidence from the United States that socioeconomic disadvantage is associated with lower use of palliative chemotherapy.[10, 210] Elderly patients with advanced cancer are also less likely to receive chemotherapy than younger patients, even though there is evidence of benefit in older patients.[218, 219] In our population-based study in Queensland and New South Wales only 43% of people diagnosed with inoperable disease received chemotherapy[293] but there are currently no recent published data about determinants of receipt of therapy. Newer chemotherapy regimens with greater impacts on survival and quality of life are now used for treatment of advanced pancreatic cancer, including FOLRIRINOX and albumin-bound paclitaxel and Gemcitabine. [151-153] Ensuring equitable access to these and other novel systemic treatments as they become available will be an important contributor to improvements in survival in the coming decade.

Conclusion

Pancreatic cancer continues to have unacceptably high mortality and patients report extremely high supportive care needs throughout the course of disease.[167] International and limited Australian data suggest that not all patients receive optimal treatment, and that variability in care may be related to socio-demographic factors. There is considerable investment in new strategies for diagnosis and treatment and there now appears to be light at the end of the tunnel. However immediate improvements could be made by implementing policies and procedures that enable all patients to be managed by high-performing multidisciplinary teams, ensuring receipt of optimal curative and supportive treatment modalities. This will also enable full realisation of benefits expected to accrue from the development of new treatments over the coming decades.

9.8. APPENDIX G

9.8.1. Chapter 7 (Quality-of-care score) supplementary tables

Table 9-6: Proportions of eligible patients for whom each quality-of-care item was met, by place of residence

Item	N eligible (% met criteria)			
	Major city	Inner regional	Rural	P value[a]
All patients with potentially resectable disease should be referred to an hepatobiliary surgeon	548 (53)	159 (52)	74 (41)	0.003
All patients with technically resectable disease should be offered a resection or have a valid reason for no surgery	368 (99)	105 (96)	154 (96)	0.10
Surgery should be performed by surgeons who perform more than 5 pancreatic surgeries per year	260 (40)	74 (57)	32 (38)	0.19
Tumour resectability should be assessed by a MDT at a tertiary hospital	548 (30)	159 (33)	74 (15)	<0.001
All patients should have a triple phase/ pancreas protocol CT scan for staging	1076 (45)	338 (36)	157 (47)	0.015
Entry into a clinical trial should be considered for all patients	1076 (7)	338 (6)	157 (2)	0.03
Surgery should take place in tertiary institutions where > 11 resections are performed annually	260 (39)	74 (53)	32 (41)	0.39
Each patient should have a care-coordinator assigned with an individualised treatment/ clinical plan	1076 (22)	338 (26)	157 (13)	0.005
Tissue diagnosis should be obtained where possible	1076 (82)	338 (78)	157 (69)	0.001
All patients should be presented to a MDT	1076 (35)	338 (26)	157 (22)	< 0.001
Biliary obstruction should routinely be managed endoscopically in non-resectable patients	286 (85)	88 (82)	42 (76)	0.78
All patients should be offered adjuvant therapy post operatively, assuming performance status is adequate	260 (67)	74 (68)	32 (66)	0.62
All patients should be offered psychosocial support	1076 (23)	338 (12)	157 (7)	< 0.001
Pancreatic enzyme replacement therapy should be considered for all patients	1076 (23)	338 (19)	157 (19)	0.20
All patients should see a medical oncologist	1076 (88)	338 (82)	157 (82)	0.004
A specialist HPB surgeon should be the initial/primary specialist unless the patient has obvious metastases	548 (23)	159 (13)	74 (3)	< 0.001
All patients should be referred to a dietitian soon after diagnosis	1076 (68)	338 (52)	157 (59)	< 0.001
Patients with confirmed metastatic disease should be referred to palliative care	528 (85)	179 (74)	83 (75)	0.004

[a]P value calculated using Pearson chi^2 to test differences between place of residence and proportion that met the criteria for each item.
MDT: Multidisciplinary team; CT: computerised tomography

Table 9-7 : Proportions of eligible patients for whom each quality-of-care item was met, by area-level socioeconomic status.

Item	N eligible (% met criteria) Quintiles of Index of Relative Socio-Economic Disadvantage scores					
	Least disadvantaged	2	3	4	Most disadvantaged	P value[a]
All patients with potentially resectable disease should be referred to a hepatobiliary surgeon	138 (55)	160 (51)	160 (42)	169 (50)	154 (59)	0.04
All patients with technically resectable disease should be offered a resection or have a valid reason for no surgery	91 (100)	111 (99)	100 (99)	115 (95)	102 (98)	0.05
Surgery should be performed by surgeons who perform more than 5 pancreatic surgeries per year	66 (68)	78 (42)	68 (29)	81 (40)	73 (38)	<0.001
Tumour resectability should be assessed by a MDT at a tertiary hospital	138 (30)	160 (34)	160 (29)	169 (28)	154 (26)	0.64
All patients should have a triple phase/ pancreas protocol CT scan for staging	266 (39)	327 (49)	322 (41)	338 (42)	318 (43)	0.17
Entry into a clinical trial should be considered for all patients	266 (8)	327 (10)	322 (6)	338 (4)	318 (5)	0.02
Surgery should take place in tertiary institutions where > 11 resections are performed annually	66 (53)	78 (44)	68 (32)	81 (33)	73 (47)	0.06
Each patient should have a care-coordinator assigned with an individualised treatment/ clinical plan	266 (20)	327 (26)	322 (21)	338 (26)	318 (17)	0.01
Tissue diagnosis should be obtained where possible	266 (87)	327 (80)	322 (78)	338 (78)	318 (76)	0.03
All patients should be presented to a MDT	266 (37)	327 (34)	322 (35)	338 (26)	318 (27)	0.01
Biliary obstruction should routinely be managed endoscopically in non-resectable patients	73 (86)	88 (83)	80 (83)	84 (86)	91 (79)	0.74
All patients should be offered adjuvant therapy post operatively, assuming performance status is adequate	66 (80)	78 (60)	68 (68)	81 (65)	73 (62)	0.20
All patients should be offered psychosocial support	266 (35)	327 (17)	322 (21)	338 (14)	318 (11)	< 0.001
Pancreatic enzyme replacement therapy should be considered for all patients	266 (27)	327 (28)	322 (17)	338 (20)	318 (19)	0.002
All patients should see a medical oncologist	266 (91)	327 (86)	322 (87)	338 (85)	318 (83)	0.05
A specialist HPB surgeon should be the initial/primary specialist unless the patient has obvious metastases	138 (25)	160 (20)	160 (13)	169 (16)	154 (20)	0.08
All patients should be referred to a dietitian soon after diagnosis	190 (71)	327 (63)	322 (60)	338 (61)	318 (65)	0.03
Patients with confirmed metastatic disease should be referred to palliative care	128 (83)	167 (84)	162 (82)	169 (80)	164 (81)	0.91

[a]P value calculated using Pearson chi^2 to test differences between quintiles of Index of Relative Socio-Economic Disadvantage scores and proportion that met the criteria for each item. MDT: Multidisciplinary team; CT: computerised tomography

Table 9-8 : Hazard ratios for the association between receipt of care for each care score item and survival in 1) all patients; 2) non-metastatic[a] and 3) metastatic patients[a] eligible for the care.

	Hazard ratio (95% CI)[b] for patients receiving item care compared to those not receiving care p value		
Item	**All patients**	**Non-metastatic**	**Metastatic**
All patients with potentially resectable disease should be referred to an hepatobiliary surgeon	0.82 (0.69, 0.96) 0.015	0.82 (0.69, 0.96) 0.015	n/a[c]
All patients with technically resectable disease should be offered a resection or have a valid reason for no surgery	1.94 (0.90, 4.15) 0.09	1.94 (0.90, 4.15) 0.09	n/a[c]
Surgery should be performed by surgeons who perform more than 5 pancreatic surgeries per year	0.83 (0.65, 1.06) 0.14	0.83 (0.65, 1.06) 0.14	n/a[c]
Tumour resectability should be assessed by a MDT at a tertiary hospital	0.93 (0.79, 1.11) 0.43	0.93 (0.79, 1.11) 0.43	n/a[c]
All patients should have a triple phase/ pancreas protocol computerised tomography (CT) scan for staging	0.90 (0.81, 1.00) 0.06	0.97 (0.83, 1.13) 0.68	0.87 (0.75, 1.01) 0.06
Entry into a clinical trial should be considered for all patients	1.01 (0.82, 1.25) 0.90	1.23 (0.87, 1.74) 0.24	0.92 (0.70, 1.21) 0.54
Surgery should take place in tertiary institutions where > 11 resections are performed annually	0.90 (0.70, 1.16) 0.43	0.90 (0.70, 1.16) 0.43	n/a[c]
Each patient should have a care-coordinator assigned with an individualised treatment/ clinical plan	1.00 (0.88, 1.13) 0.98	0.98 (0.81, 1.18) 0.84	0.98 (0.83, 1.17) 0.86
Tissue diagnosis should be obtained where possible	0.66 (0.57, 0.77) <0.001	0.59 (0.47, 0.75) <0.001	0.70 (0.58, 0.84) <0.001
All patients should be presented to a MDT	0.86 (0.77, 0.96) 0.01	0.89 (0.76, 1.05) 0.17	0.84 (0.72, 0.99) 0.04
Biliary obstruction should routinely be managed endoscopically in non-resectable patients	0.97 (0.74, 1.27) 0.82	1.10 (0.72, 1.70) 0.66	0.84 (0.59, 1.21) 0.35
All patients should be offered adjuvant therapy post operatively, assuming performance status is adequate	0.43 (0.33, 0.56) <0.001	0.43 (0.33, 0.56) <0.001	n/a[c]
All patients should be offered psychosocial support	1.24 (1.09, 1.12) 0.001	1.46 (1.20, 1.76) <0.001	1.05 (0.87, 1.26) 0.62
Pancreatic enzyme replacement therapy should be considered for all patients	0.83 (0.73, 0.94) 0.005	0.82 (0.69, 0.97) 0.02	0.83 (0.66, 1.00) 0.05
All patients should see a medical oncologist	1.04 (0.88, 1.23) 0.63	0.98 (0.79, 1.22) 0.85	1.06 (0.82, 1.36) 0.65
A specialist hepatobiliary surgeon should be the initial/primary specialist unless the patient has obvious metastases	0.95 (0.77, 1.17) 0.62	0.95 (0.77, 1.17) 0.62	n/a[c]
All patients should be referred to a dietitian soon after diagnosis	1.00 (0.90, 1.12) 0.98	0.96 (0.80, 1.14) 0.65	1.01 (0.87, 1.17) 0.90
Patients with confirmed metastatic disease should be referred to palliative care	1.42 (1.17, 1.74) 0.001	n/a[c]	1.42 (1.17, 1.74) 0.001

[a] according to clinical staging; [b] adjusted for age, performance status, comorbidities and clinical stage; [c] n/a: not applicable; MDT: multidisciplinary team

9.9. APPENDIX H

9.9.1. Introduction

This work was published in the Journal of Gastrointestinal Surgery. The aim of this publication was to determine mortality and complication rates following surgery and factors associated with these rates including hospital- and surgeon-case volume.

9.9.2. Contribution of candidate

My contribution to this study included research question conceptualisation (20%), data collection (15%), data cleaning (80%), data analysis (20%), interpretation of the results (20%) and writing and editing the publication (20%) with the majority of the work completed by MAW under the guidance of REN with valuable comments from the study team.

9.9.3. Manuscript

The following manuscript was published in the Journal of Gastrointestinal Surgery:

J Gastrointest Surg. 2016; 20 (8):1471-81

Determinants of outcomes following resection for pancreatic cancer - a population-based study

Mary A Waterhouse, Elizabeth A Burmeister, Dianne L O'Connell, Emma L Ballard, Susan J Jordan, Neil D Merrett, David Goldstein, David Wyld, Monika Janda, Vanessa L Beesley, Madeleine E Payne, Helen M Gooden, Rachel E Neale. .

ABSTRACT

Background

Patient and health system determinants following pancreatic cancer resection, particularly the relative importance of hospital and surgeon volume, are unclear. Our objective was to identify patient, tumour and health-service factors related to mortality and survival among a cohort of patients who underwent completed resection for pancreatic cancer.

Methods

Eligible patients were diagnosed with pancreatic adenocarcinoma between July 2009 and June 2011, and had a completed resection performed in Queensland or New South Wales, Australia, with either tumour-free (R0) or microscopically involved margins (R1) (n = 270).

Associations were examined using logistic regression (for binary outcomes) and Cox proportional hazards or stratified Cox models (for time-to-event outcomes).

Results

Patients treated by surgeons who performed < 4 resections/year were more likely to die from a surgical complication (versus ≥ 4 resections/year, $P = 0.04$), had higher one-year mortality ($P = 0.03$), and worse overall survival up to 1.5 years after surgery (adjusted hazard ratio 1.58, 95% confidence interval 1.07-2.34). Among patients who had ≥ 1 complication within 30 days of surgery, those aged ≥ 70 years had higher one-year mortality compared to patients aged < 60 years. Adjuvant chemotherapy treatment improved recurrence-free survival (P = 0.01). There were no significant associations between hospital volume and mortality or survival.

Conclusions

Systems should be implemented to ensure that surgeons are completing a sufficient number of resections to optimize patient outcomes. These findings may be particularly relevant for countries with a relatively small and geographically dispersed population.

INTRODUCTION

Pancreatic cancer has the worst survival of any cancer. The only potentially curative option is surgical removal of the tumour.[86] Surgery is technically demanding and may require complex vascular reconstructions and is associated with significant morbidity and mortality. However, successful resection combined with multimodality therapy improves five-year survival from 5%[324] to more than 20%.[86]

Lymph node positivity ratio (number of positive lymph nodes divided by total number of nodes examined), treatment with adjuvant chemotherapy and pathologic T stage were the three most important predictors of long-term survival (≥ 10 years from diagnosis) after resection surgery in a recent, large study.[325] Poor tumour differentiation[325-327] and involved margins[325, 326, 328-330] are associated with poor prognosis, and worse outcomes have been reported for older patients[331, 332] and those with a lower socioeconomic status (SES).[327]

Convincing evidence of an association between increasing hospital volume (number of attempted resections/year) and both lower short-term mortality[114, 333-335] and better long-term survival[114] after pancreatic surgery has led to a push for greater centralisation of care. Also, some studies have reported better outcomes with increasing surgeon volume.[133, 138, 336] It has been suggested that higher volume providers may have lower rates of involved margins[128] and complications,[337, 338] use multi-modal therapies more extensively,[13] or offer superior post-operative care.[86] Alternatively, the associations might reflect differences in case-mix.

We used data from an Australian population-based study of patients with pancreatic cancer to identify patient, tumour and health-service factors related to mortality and survival following completed resection. We also examined associations with margins and complications, which may mediate effects on mortality and survival.

METHODS

Study sample and data collection

A detailed description of the study sample, ethics approval and data collection methods has been published.[339] Briefly, the study sample comprised patients aged ≥ 18 years who were diagnosed with pancreatic ductal adenocarcinoma or pancreatic cancer of unknown morphological subtype (ICD-10 code C25) between 1 July 2009 and 30 June 2011 and notified to the Queensland (QLD) Cancer Registry, or between 1 July 2009 and 31 December 2010 and notified to the New South Wales (NSW) Central Cancer Registry. We obtained demographic data and details regarding the initial diagnosis from the cancer registries, and trained research nurses collected clinical data from medical records. Date of death was obtained from either the medical records or cancer registries.

Outcomes

Overall survival (OS) was defined as the number of months from surgery until death from any cause or, if the person did not die, until the end of the study (25 February 2014). Recurrence-free survival (RFS) was defined as the number of months from surgery until recurrence (the first date that imaging detected metastases or disease at the primary site) or death or, if neither occurred, until the end of the study. We analysed death from surgical complications, 90-day and one-year mortality (from date of surgery), complications within 30 days of surgery (any complication, wound infection, intra-abdominal sepsis, anastomotic leak and haemorrhage), and margin status as binary outcomes. Margin status was categorised into involved or clear < 1 mm (reference category) and clear ≥ 1 mm.[340]

Factors of interest

Factors analysed included age at diagnosis, area-level socioeconomic status (SES), place of residence, Charlson comorbidity index, Eastern Cooperative Oncology Group (ECOG) performance status, preoperative assumed tumour status (i.e. clinical stage: confined to pancreas or locally advanced), TNM stage (Union for International Cancer Control (UICC) 7th Edition),[81] presence of positive lymph nodes, tumour differentiation, tumour site, pre-operative white blood cell (WBC) count and albumin level, time from diagnosis to resection, hospital type where surgery was performed (public or private), complications within 30 days of surgery, margin status, adjuvant chemotherapy treatment, surgeon volume, hospital volume, and combined hospital and surgeon volume.

SES was assigned based on residential location, and remoteness of place of residence was measured using the Accessibility/Remoteness Index of Australia. Categorisation of these was described previously.[339] Surgical volume, calculated as the number of attempted resections in our dataset performed per year, was categorised as high-volume (HV) and low-volume (LV). The thresholds used to define HV were ≥ 4 and ≥ 6 resections/year for surgeon volume and hospital volume, respectively. These were chosen primarily to enable robust statistical analyses, but we explored a range of other cut points and found no change in our conclusions.

Exclusions

We restricted analyses of outcomes to 270 patients who had a completed resection performed in NSW or QLD, with either tumour-free (R0) or microscopically involved margins (R1) (n = 270). Nine patients who died during their surgical resection admission (n = 9) were excluded from analyses of recurrence and analyses where the factor of interest was adjuvant chemotherapy treatment.

Statistical analysis

Chi-squared tests (and Fisher's exact test, as required) were used to examine associations between factors. Logistic regression was used to estimate crude and adjusted odds ratios (ORs, AORs). To test whether the association between age and mortality was modified by complications (none, any within 30 days of surgery), we included an interaction term for age by complications, and analyses were repeated within strata defined by complications.

Median survival and survival curves were estimated using Kaplan-Meier methods. We used Cox proportional hazards (PH) or stratified Cox models to estimate crude and adjusted hazard ratios (HRs, AHRs). The PH assumption was assessed using log-log survival curves and Schoenfeld residuals. Since the OS curves for any complication within 30 days of surgery, age, and surgeon volume appeared to converge over time (Figures 1A to 1C), we partitioned survival time into two intervals (before and after a specified time point) and used an extended Cox model to estimate a constant HR for each interval. Models were fitted using different time points; the value used in the final model was the maximum number of months for which the 95% confidence interval (CI) for the HR in the first time interval did not contain one.

We used directed acyclic graphs to guide selection of potential confounding factors to be included in adjusted models.[341] For associations between surgeon or hospital volume and outcomes (excluding complications), we also fitted models with a continuous propensity score as the only adjustment variable. Propensity scores were estimated using logistic regression models that included age, sex, state and remoteness of residence, SES, smoking status, family history of cancer, Charlson comorbidity index, ECOG performance status, TNM stage, positive lymph nodes, tumour differentiation and site, pre-operative WBC count and albumin level, jaundice and weight loss at diagnosis, any stenting prior to resection surgery, and hospital type. We also estimated a propensity score for chemotherapy treatment using the model above but with pre-operative WBC and albumin level omitted, and surgeon/hospital volume, any complications, and total length of stay included. Fit was assessed using the C-statistic of the receiver operating characteristic curve.

When analysing surgeon or hospital volume, we accounted for patient clustering using generalised estimating equations with an exchangeable correlation matrix or robust sandwich estimates of standard errors. Statistical analyses were performed in SAS version 9.4 (SAS Institute, Inc, Cary, NC). Figures were produced using the survival package (version 2.38) in R.[342] All P-values are two-sided and we used a statistical significance level of $P < 0.05$.

RESULTS

Of 369 attempted resections, 365 were performed in NSW or QLD, of which 87 (24%) were aborted. There were no associations between patient or health system factors and whether or not the surgery was completed. A further eight patients were excluded because distant metastases were found during surgery, leaving 270 patients (average age 64 years, 63% men) for analyses of surgical outcomes. Characteristics of these patients are shown in the second column of Table 9-9.

Table 9-9: Patient and tumour characteristics

	All attempted resections (n=365)	Completed resections (n=278)	Aborted resections (n=87)
Variable	**N (%)**	**N (%)**	**N (%)**
Sex			
Male	220 (60)	174 (63)	46 (53)
Female	145 (40)	104 (37)	41 (47)
Age at diagnosis, years			
<60	104 (28)	79 (28)	25 (29)
60-69	133 (36)	101 (36)	32 (37)
≥70	128 (35)	98 (35)	30 (34)
Place of residence			
Major City	258 (71)	199 (72)	59 (69)
Inner Regional	73 (20)	53 (19)	20 (23)
Outer regional/remote[a]	32 (9)	25 (9)	7 (8)
Missing	2	1	1
Socioeconomic status - quintiles			
Most disadvantaged	74 (20)	62 (22)	12 (14)
Second	81 (22)	60 (22)	21 (24)
Third	67 (18)	47 (17)	20 (23)
Fourth	75 (21)	55 (20)	20 (23)
Least disadvantaged	66 (18)	53 (19)	13 (15)
Missing	2	1	1
TMN Stage			
Stage I	36 (10)	35 (13)	1 (1)
Stage II	257 (71)	227 (83)	30 (34)
Stage III	23 (6)	3 (1)	20 (23)
Stage IV	44 (12)	8 (3)	36 (41)
Missing	5	5	0
Positive lymph nodes			
No	112 (34)	91 (33)	21 (35)
Yes	221 (66)	182 (67)	39 (65)
Missing	32	5	27

Variable	All attempted resections (n=365) N (%)	Completed resections (n=278) N (%)	Aborted resections (n=87) N (%)
Tumour site			
Uncinate process	77 (22)	56 (21)	21 (25)
Head	209 (59)	159 (58)	50 (59)
Neck	11 (3)	9 (3)	2 (2)
Body	28 (8)	17 (6)	11 (13)
Tail	32 (9)	31 (11)	1 (1)
Missing	8	6	2
Was tumour considered resectable?			
No[b]	5 (1)	1 (0.4)	4 (5)
Yes, confined to pancreas	148 (41)	120 (43)	28 (32)
Yes, locally advanced	199 (55)	146 (53)	53 (61)
Yes, no other details	12 (3)	10 (4)	2 (2)
Missing	1	1	0
Charlson Comorbidity Index (score)			
Low (0)	183 (50)	143 (52)	40 (46)
Medium (1)	106 (29)	81 (29)	25 (29)
High (≥2)	74 (20)	52 (19)	22 (25)
Missing	2	2	0
ECOG performance status			
Fully active	184 (58)	145 (59)	39 (53)
Not fully active	134 (42)	99 (41)	35 (47)
Missing	47	34	13

[a] Includes very remote locations. [b] Resection attempted even though the tumour was thought to be non-resectable on staging
ECOG, Eastern Cooperative Oncology Group; TNM, tumour node metastases

Sixteen of 50 hospitals and 14 of 79 surgeons were categorised as HV providers. Concordance between hospital volume and surgeon volume is shown in Table 2. The C-statistic for the propensity score models for both surgeon and hospital volume was 0.80, and for chemotherapy treatment it was 0.86. A greater percentage of patients treated by LV surgeons were aged ≥ 70 years (versus HV: 43% versus 28%), and HV hospitals were more likely to treat patients with TNM stage II/III tumours (versus LV: 90% versus 79%) (Table 9-10).

Table 9-10: Selected patient and tumour characteristics classified by surgeon and hospital volume[a] and hospital type (n=270)[b]: chi-squared test.

	N (%)									
		Surgeon volume			Hospital volume			Hospital type		
	Overall	High (*n*=144)	Low (*n*=126)	p-value	High (*n*=184)	Low (*n*=86)	p-value	Public (*n*=164)	Private (*n*=106)	p-value
Age at diagnosis, years										
<60	77 (29)	38 (26)	39 (31)	0.003	50 (27)	27 (31)	0.47	47 (29)	30 (28)	0.33
60-69	99 (37)	66 (46)	33 (26)		72 (39)	27 (31)		55 (34)	44 (42)	
≥70	94 (35)	40 (28)	54 (43)		62 (34)	32 (37)		62 (38)	32 (30)	
Charlson comorbidity index (score)										
Low (0)	139 (52)	75 (52)	64 (52)	0.50	98 (53)	41 (49)	0.70	78 (48)	61 (59)	0.18
Medium (1)	79 (29)	39 (27)	40 (32)		54 (29)	25 (30)		54 (33)	25 (24)	
High (≥ 2)	50 (19)	30 (21)	20 (16)		32 (17)	18 (21)		32 (20)	18 (17)	
ECOG performance status										
Fully active	139 (59)	84 (62)	55 (54)	0.23	102 (62)	37 (52)	0.16	70 (50)	69 (73)	<0.001
Not fully active	97 (41)	51 (38)	46 (46)		63 (38)	34 (48)		71 (50)	26 (27)	
Tumour site										
Head/Neck/Uncinate process	218 (83)	124 (86)	94 (78)	0.10	152 (84)	66 (80)	0.38	134 (85)	84 (79)	0.24
Body/Tail	46 (17)	20 (14)	26 (22)		29 (16)	17 (20)		24 (15)	22 (21)	
Pre-operative tumour status[c]										
Confined	119 (46)	64 (46)	55 (46)	0.94	77 (43)	42 (53)	0.12	62 (39)	57 (55)	0.01
Locally advanced	140 (54)	76 (54)	64 (54)		103 (57)	37 (47)		97 (61)	47 (45)	
TNM stage										
I	35 (13)	16 (11)	19 (15)	0.32	18 (10)	17 (21)	0.02	17 (11)	18 (17)	0.13
II/III[d]	230 (87)	126 (89)	104 (85)		165 (90)	65 (79)		143 (89)	87 (83)	

[a] Surgeon volume classified as high (≥ 4) and low (<4 resections/year). Hospital volume classified as high (≥ 6) and low (<6 resections/year).
[b] Analysis based on 270 people who had a completed resection and were not found to have distant metastases.
[c] Confined: Considered resectable and confined to pancreas; Locally advanced: consider non-resectable or considered resectable and locally advanced. ECOG, Eastern Cooperative Oncology Group.
[d] Only 3 people had a TNM stage III tumour.

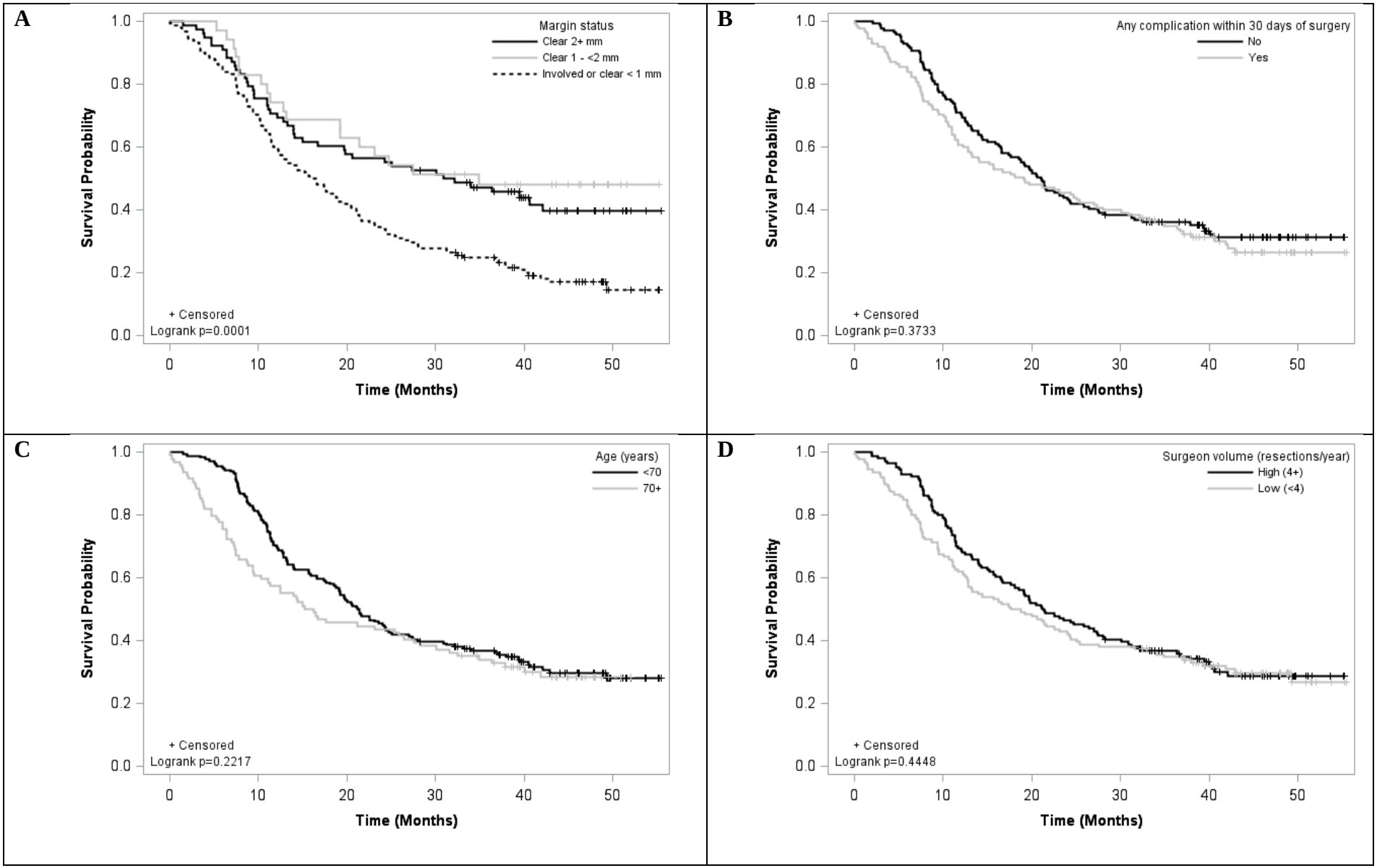
Mortality, overall and recurrence-free survival

Nine patients (3%) died during their index admission; eight of these deaths were attributed to surgical complications and seven of the eight patients were aged 70 years or over. The percentages of patients dying within 90 days and one year of surgery were 4% (n = 12) and 34% (n = 93), respectively. Cause of death was not stated for three patients. Cancer progression was the most common cause of death within one year of surgery (n=79, 88%), followed by surgical complications (n=8, 9%). Median OS and RFS were 20 and 13 months, respectively.

Ninety-day mortality was higher for patients who were older (≥ 70 versus < 60 years, 11% versus 1%), had poor ECOG performance status (not fully active versus fully active, 7% versus 1%), or had ≥ 1 complication within 30 days of surgery (versus none, 8% versus 1%) (all $P < 0.05$). Patients treated by LV surgeons had higher 90-day mortality, although this was not statistically significant (7% in LV versus 2% in HV, $P = 0.10$).

One-year mortality was higher and OS was lower for patients with positive lymph nodes, margins that were involved or clear < 1 mm, and with declining performance status (Table 9-11). Only 13% of patients had stage I disease and they had better OS than patients with stage II/III disease.

Patients who had ≥ 1 complication within 30 days of surgery had a greater hazard of dying in the first 8 months following surgery but there was no difference after 8 months (< 8 months: AHR 1.79, 95% CI 1.04-3.08, ≥ 8 months: AHR 0.94, 95% CI 0.66-1.34); OS continued to appear worse up to 16 months following surgery, but this difference was not statistically significant (< 16 months: AHR 1.34, 95% CI 0.93-1.95) (Figure 9-1).


A
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Margin status
Clear 2+ mm
Clear 1 - <2 mm
Involved or clear < 1 mm
+ Censored
Logrank p=0.0001
0
10
20
30
40
50
Time (Months)
B
Survival Probability
Any complication within 30 days of surgery
No
Yes
+ Censored
Logrank p=0.3733
Time (Months)
C
Survival Probability
Age (years)
<70
70+
+ Censored
Logrank p=0.2217
Time (Months)
D
Survival Probability
Surgeon volume (resections/year)
High (4+)
Low (<4)
+ Censored
Logrank p=0.4448
Time (Months)

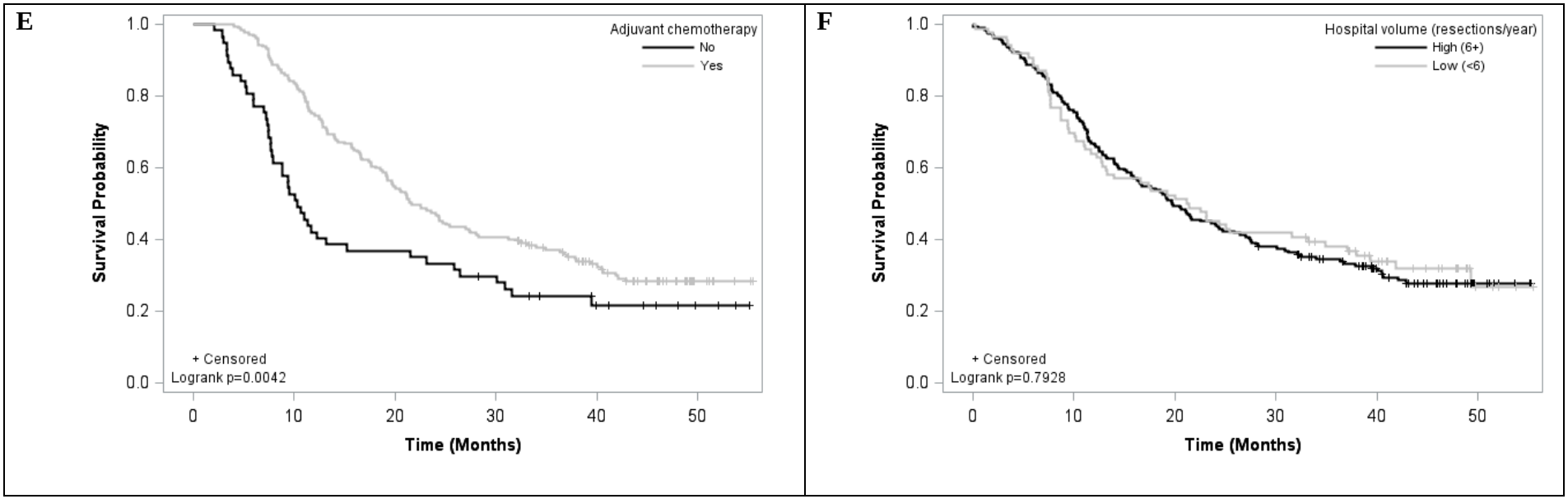


Figure 9-1: Kaplan-Meier survival curves by margin status (A), any complication within 30 days of surgery (B), age at diagnosis (C), surgeon volume (D), adjuvant chemotherapy (E), and hospital volume (F) for people who had a completed resection for pancreatic cancer and who were not found to have distant metastases during surgery (n=270).

Compared with patients who did not have adjuvant chemotherapy treatment, those who received treatment had lower odds of dying within one year (AOR 0.33, 95% CI 0.16-0.69). Using the standard model the AHR was not statistically significant, but when a propensity score-adjusted model was fitted, patients who received chemotherapy treatment had improved OS (versus no treatment: AHR 0.51, 95% CI 0.34-0.76). However, these results should be interpreted with caution because the PH assumption was violated (i.e., the HRs may vary with time).

Patients who were older, had more comorbidities, or lived in the most disadvantaged SES areas had a greater likelihood of dying within one year of surgery (Table 9-11). There was significant interaction between age and any complication occurring within 30 days of surgery ($P = 0.005$). Among patients who had ≥ 1 complication, those aged ≥ 70 years had greater odds of dying within one year (versus < 60 years: 61% versus 26%, OR 4.41, 95% CI 1.67-11.69); 27% of deaths in those aged ≥ 70 years were due to surgical complications whereas nobody aged < 60 years died from surgical complications. In contrast, one-year mortality did not differ by age amongst patients who did not have any complications ($P = 0.35$). Compared to patients aged < 70 years, patients aged ≥ 70 years had worse OS up to 19 months following surgery (HR 1.55, 95% CI 1.09-2.21) (Figure 9-1).

We examined the effects of SES further by comparing patients living in the most disadvantaged areas with all other patients (reference group). Those living in the most disadvantaged areas were less likely to see a medical oncologist (85% versus 96%) and to be offered (79% versus 92%) or receive (62% versus 76%) adjuvant chemotherapy treatment (all $P < 0.05$), but they were no less likely to see a HV surgeon (53% versus 54%, $P = 0.86$). Adjustment for chemotherapy treatment slightly attenuated the association with one-year mortality (unadjusted OR 2.47, 95% CI 1.37-4.46; with adjustment, AOR 2.16, 95% CI 1.15-4.05), whereas the estimated OR was not meaningfully changed after adjustment for TNM stage, Charlson comorbidity index, performance status, hospital type, or age (data not shown).

Patients operated on by a LV surgeon were more likely to die from a surgical complication (versus HV: 5.6% versus 0.7%, $P = 0.04$), and had higher one-year mortality (AOR 1.75, 95% CI 1.06-2.87) (Table 9-11). The association was stronger when a propensity score-adjusted model was fitted (AOR 1.99, 95% CI 1.07-3.70), but not statistically significant after adjusting for any complications within 30 days of surgery ($P \geq 0.10$ for both standard and propensity score analyses). Using an extended Cox model, we found that OS was statistically significantly worse up to 19 months following surgery for patients who were operated on by a LV surgeon (AHR 1.58, 95% CI 1.07-2.34), after which time surgeon volume was not associated with OS (AHR 0.97, 95% CI 0.56-1.68) (Figure 9-1).

Table 9-11: Associations between selected exposure variables and mortality[a] and overall survival[b] (n=270)[c]: logistic regression, Cox proportional hazards and stratified Cox models[d].

		1-year mortality (deaths=93) [a]			Overall survival [b]		
Exposure variable	**N (%)**	**% dead**	**Crude OR (95% CI)**	**Adjusted OR (95% CI) [e]**	**Median (months)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI) [e]**
Age at diagnosis, years							
<60	77 (29)	27.3	1	1	23.5	1[f]	1[f]
60-69	99 (37)	32.3	1.27 (0.66, 2.45)	1.27 (0.66, 2.45)	19.7	1.15 (0.80, 1.66)	1.15 (0.80, 1.66)
≥70	94 (35)	42.6	1.98 (1.03, 3.77)	1.98 (1.03, 3.77)	15.7	1.31 (0.91, 1.88)	1.31 (0.91, 1.88)
p-value, p-trend			0.10, 0.03	0.10, 0.03		0.36, 0.15	0.36, 0.15
Socioeconomic status - quintiles							
Most disadvantaged	59 (22)	50.8	1	1	11.4	1	1
Second	59 (22)	30.5	0.42 (0.20, 0.90)	0.42 (0.20, 0.90)	21.4	0.79 (0.51, 1.23)	0.79 (0.51, 1.23)
Third	47 (17)	27.7	0.37 (0.16, 0.84)	0.37 (0.16, 0.84)	21.1	0.77 (0.48, 1.22)	0.77 (0.48, 1.22)
Fourth	54 (20)	24.1	0.31 (0.14, 0.69)	0.31 (0.14, 0.69)	25.7	0.76 (0.49, 1.18)	0.76 (0.49, 1.18)
Least disadvantaged	50 (19)	36.0	0.54 (0.25, 1.18)	0.54 (0.25, 1.18)	19.2	0.89 (0.57, 1.40)	0.89 (0.57, 1.40)
p-value, p-trend			0.03, 0.06	0.03, 0.06		0.71, 0.58	0.71, 0.58
Place of residence							
Major City	192 (71)	33.3	1	1	22.8	1	1
Inner Regional	52 (19)	34.6	1.06 (0.56, 2.02)	1.16 (0.58, 2.34)	18.4	1.15 (0.80, 1.65)	1.14 (0.79, 1.65)
Outer regional/remote/very remote	25 (9)	40.0	1.33 (0.57, 3.13)	1.70 (0.65, 4.44)	15.7	1.35 (0.83, 2.19)	1.43 (0.86, 2.39)
p-value			0.80	0.54		0.41	0.35
Charlson comorbidity index (score)							
Low (0)	139 (52)	32.4	1	1	21.1	1	1
Medium (1)	79 (29)	29.1	0.86 (0.47, 1.57)	0.72 (0.38, 1.38)	25.4	0.83 (0.59, 1.16)	0.77 (0.53, 1.11)
High (≥ 2)	50 (19)	50.0	2.09 (1.08, 4.04)	2.09 (1.05, 4.18)	12.3	1.27 (0.87, 1.85)	1.22 (0.82, 1.82)
p-value			0.04	0.02		0.14	0.11
ECOG performance status							
Fully active	139 (59)	25.9	1	1	25.8	1[f]	1[f]
Not fully active	97 (41)	44.3	2.28 (1.31, 3.96)	2.25 (1.28, 3.98)	13.3	1.63 (1.19, 2.21)	1.61 (1.18, 2.19)
p-value			0.004	0.01		0.002	0.003

		1-year mortality (deaths=93) [a]			Overall survival [b]		
Exposure variable	**N (%)**	**% dead**	**Crude OR (95% CI)**	**Adjusted OR (95% CI) [e]**	**Median (months)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI) [e]**
TNM stage [h]							
I	35 (13)	22.9	1	1	30.3 [g]	1	1
II/III	230 (87)	36.1	1.91 (0.83, 4.39)	1.91 (0.83, 4.39)	19.2	2.26 (1.33, 3.83)	2.26 (1.33, 3.83)
p-value			0.13	0.13		0.003	0.003
Positive lymph nodes							
No	90 (34)	21.1	1	1	41.9	1	1
Yes	175 (66)	41.1	2.61 (1.45, 4.71)	2.61 (1.45, 4.71)	16.6	2.15 (1.54, 3.02)	2.15 (1.54, 3.02)
p-value			0.001	0.001		<0.0001	<0.0001
Poorly differentiated / undifferentiated tumour							
No	83 (63)	36.1	1	1	22.5	1	1
Yes	49 (37)	38.8	1.12 (0.54, 2.32)	1.12 (0.54, 2.32)	14.0	1.30 (0.86, 1.95)	1.30 (0.86, 1.95)
p-value			0.76	0.76		0.22	0.22
Tumour site							
Head/Neck/Uncinate process	218 (83)	35.3	1	1	19.2	1	1
Body/Tail	46 (17)	32.6	0.89 (0.45, 1.74)	0.89 (0.45, 1.74)	30.4	0.73 (0.49, 1.10)	0.73 (0.49, 1.10)
p-value			0.73	0.73		0.13	0.13
Hospital type							
Public	164 (61)	35.4	1	1	19.5	1	1
Private	106 (39)	33.0	0.90 (0.54, 1.51)	1.14 (0.65, 2.02)	21.5	0.88 (0.66, 1.19)	0.99 (0.72, 1.37)
p-value			0.69	0.65		0.41	0.95
Any complications within 30 days of surgery							
No	141 (53)	29.8	1	1	21.1	1	1
Yes	125 (47)	39.2	1.52 (0.91, 2.53)	1.46 (0.87, 2.45)	19.1	1.14 (0.85, 1.52)	1.15 (0.85, 1.54)
p-value			0.11	0.15		0.37	0.37
Margin status [i]							
Involved or clear < 1 mm	148 (57)	40.5	1	1	16.2	1	1
Clear ≥ 1 mm	113 (43)	28.3	0.58 (0.34, 0.98)	0.57 (0.32, 0.99)	32.1	0.52 (0.38, 0.71)	0.49 (0.36, 0.67)
p-value			0.04	0.04		<0.0001	<0.0001

		1-year mortality (deaths=93) [a]			Overall survival [b]		
Exposure variable	**N (%)**	**% dead**	**Crude OR (95% CI)**	**Adjusted OR (95% CI) [e]**	**Median (months)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI) [e]**
Treated with adjuvant chemotherapy [j]							
No	57 (24)	57.9	1	1	10.3	1[f]	1[f]
Yes	177 (76)	25.4	0.25 (0.13, 0.46)	0.33 (0.16, 0.69)	21.6	0.61 (0.43, 0.86)	0.72 (0.48, 1.08)
p-value			<0.0001	0.003		0.005	0.11
Surgeon volume, resections/year							
≥ 4	144 (53)	31.3	1	1	21.3	1[f]	1
< 4	126 (47)	38.1	1.33 (0.80, 2.22)	1.75 (1.06, 2.87)	18.2	1.12 (0.84, 1.49)	1.14 (0.80, 1.63)
p-value			0.27	0.03		0.44	0.45
Hospital volume, resections/year							
≥ 6	184 (68)	33.7	1	1	19.8	1	1
< 6	86 (32)	36.0	1.09 (0.60, 1.98)	1.00 (0.52, 1.93)	21.3	0.96 (0.68, 1.35)	0.99 (0.67, 1.44)
p-value			0.79	0.99		0.81	0.94
Combined surgeon and hospital volumes, resections/year							
≥ 4 and ≥ 6 (both high)	130 (48)	29.2	1	1	21.5	1[f]	1
≥ 4 and < 6	14 (5)	50.0	2.70 (0.75, 9.74)	1.17 (0.27, 5.11)	14.7	1.12 (0.49, 2.54)	0.78 (0.29, 2.07)
< 4 and ≥ 6	54 (20)	44.4	2.14 (1.11, 4.15)	1.62 (0.71, 3.68)	13.6	1.31 (0.86, 1.99)	1.19 (0.76, 1.84)
< 4 and < 6 (both low)	72 (27)	33.3	1.32 (0.76, 2.28)	1.22 (0.63, 2.39)	22.0	1.02 (0.71, 1.46)	1.08 (0.73, 1.60)
p-value			0.08	0.72		0.65	0.82

[a] Crude and adjusted odds ratios (ORs) calculated using logistic regression.

[b] Median survival calculated using Kaplan-Meier methods. Crude hazard ratios (HRs) calculated using Cox proportional hazards (PH) models. Adjusted HRs calculated using Cox PH or stratified Cox models.

[c] Restricted to patients who had a completed resection and who were not found to have distant metastases during surgery.

[d] When analysing associations with hospital and surgeon volume, we adjusted for patient clustering using GEEs with an exchangeable correlation matrix (mortality) and robust sandwich estimates of standard errors (overall survival).

[e] Adjustment variables: **Age, Socio-economic status, TNM stage, Positive lymph nodes, Poorly differentiated / undifferentiated tumour, Tumour site** – none; **Place of residence** – age at diagnosis, Charlson comorbidity index and adjuvant chemotherapy treatment; **Charlson comorbidity index** – age at diagnosis and socio-economic status; **ECOG performance status** – age at diagnosis and Charlson comorbidity index; **Hospital type** – age at diagnosis, Charlson comorbidity index, ECOG performance status, TNM stage and hospital volume; **Any complication** – surgeon volume and hospital volume; **Margin status** – age at diagnosis, Charlson comorbidity index, ECOG performance status and TNM stage; **Treated with adjuvant chemotherapy** – age at diagnosis, Charlson comorbidity index, ECOG performance status, TNM stage, any complication within 30 days of surgery

and total length of stay; **Surgeon volume, Hospital volume, Combined surgeon and hospital volumes** – age at diagnosis, Charlson comorbidity index, ECOG performance status, TNM stage and adjuvant chemotherapy treatment.

[f] PH assumption violated for exposure variable.

[g] Median value not available due to censoring; mean survival given instead.

[h] Only 3 people had a TNM stage III tumour.

[i] "Clear margins, distance not stated" assumed to be clear ≥ 1 mm.

[j] Excludes patients who died during their acute admission.

ECOG, Eastern Cooperative Oncology Group; GEE, generalised estimating equation; TNM, tumour node metastases.

In neither standard models (Table 9-11) nor propensity score-adjusted models (data not shown) was there an association between hospital volume and one-year mortality or OS (Figure 9-1); associations remained statistically non-significant after including surgeon volume as a potential confounder (data not shown). Mortality and OS were not associated with place of residence, tumour differentiation or site, hospital type, combined hospital and surgeon volume (Table 9-11), WBC count, albumin level or time from diagnosis to surgery (data not shown, OS: all P > 0.50). Results for RFS were similar to those for OS Of interest, however, chemotherapy treatment conferred a benefit (versus no treatment: median RFS, 14.3 versus 6.0 months; AHR 0.59, 95% CI 0.39-0.88 [standard model]; AHR 0.42, 95% CI 0.28-0.64 [propensity score-adjusted model]) (Table 9-14).

Complications and margin status

Approximately half (47%) of all patients experienced ≥ 1 complication within 30 days of resection. LV surgeons had statistically non-significantly higher rates of any complications within 30 days (versus HV, 52% versus 42%, P = 0.17) (see Supplementary Table 4). The three most common complications were intra-abdominal sepsis (n=37), wound infection (n=27) and anastomotic leak (n=27). Wound infections were more common for LV surgeons (15% versus 6%) and LV hospitals (versus HV: 17% versus 7%), and LV surgeons had higher rates of intra-abdominal sepsis (20% versus 9%) (all $P < 0.05$). There were no statistically significant associations with anastomotic leak or haemorrhage.

Of the 261 patients with a valid margin status, 43% (n = 113) had margins that were clear ≥ 1 mm. Preoperative assumed tumour status was the only factor statistically significantly associated with margin status; 36% of patients with locally advanced tumours had clear margins compared with 53% of those with confined disease (P = 0.01) (Table 9-12). Propensity score adjustment did not meaningfully change estimates of association between surgeon / hospital volume and margin status.

Table 9-12: Associations between selected exposure variables[a] and margin status (n=261)[b]: logistic regression[c].

		Clear ≥1 mm (n=113)		
Exposure variable	**N (%)**	**N (%)[d]**	**Crude OR (95% CI)**	**Adjusted OR (95% CI) [e]**
Preoperative assumed tumour status				
Confined to pancreas	117 (46)	39.3	1	1
Locally advanced	138 (54)	39.1	0.49 (0.30, 0.81)	0.50 (0.30, 0.83)
p-value			0.01	0.01
Hospital type				
Public	155 (59)	38.1	1	1
Private	106 (41)	38.7	1.58 (0.96, 2.61)	1.44 (0.85, 2.45)
p-value			0.07	0.17
Surgeon volume, resections/year				
≥ 4	142 (54)	38.0	1	1
< 4	119 (46)	38.7	0.82 (0.46, 1.47)	0.84 (0.48, 1.47)
p-value			0.51	0.54
Hospital volume, resections/year				
≥ 6	180 (69)	38.3	1	1
< 6	81 (31)	38.3	0.83 (0.43, 1.60)	0.93 (0.46, 1.84)
p-value			0.58	0.83

[a] Data not shown for age at diagnosis, socioeconomic status, place of residence or tumour site; all p>0.15.
[b] Restricted to people who had a completed resection, who were not found to have distant metastases, and who had complete margins data. Nine people had missing margins data.
[c] Margins that were involved or clear <1 mm is the reference group. When analysing associations with hospital and surgeon volume, we adjusted for patient clustering using GEEs with an exchangeable correlation matrix.
[d] Row percentages.
[d] Adjustment variables: **Pre-operative tumour status –** hospital volume; **Hospital type** – pre-operative tumour status and hospital volume; **Surgeon volume** – pre-operative tumour status; **Hospital volume** – hospital type, pre-operative tumour status and surgeon volume.
GEE, generalised estimating equation.

DISCUSSION

Consistent with the international literature, OS was worse for patients with declining performance status, unfavourable tumour characteristics or margins that were involved or clear < 1mm, and patients who had adjuvant chemotherapy treatment had better RFS. Older patients had higher one-year mortality, but the association between age and OS diminished with time from surgery. Patients treated by LV surgeons had higher 90-day and one-year mortality and worse OS up to 1.5 years after surgery, but there were no significant associations between hospital volume and mortality or survival.

Of the tumour factors considered, lymph node positivity showed the strongest association with higher mortality and lower survival, consistent with expectations.[86, 325] Similarly, the survival advantage observed for patients with stage I disease was not surprising. We did not confirm an association between poorly differentiated or undifferentiated tumours and worse outcomes,[325-327] most likely due to missing data for this factor. We also found no associations with tumour site; this is consistent with some findings,[325, 343, 344] although others have found that those with tumours of the body or tail (versus head) had both worse[328, 345, 346] and better[22] survival.

While age alone does not seem to be a contraindication to surgery,[327, 347, 348] our findings suggest that complications have a more deleterious effect on older patients. Since patients treated by HV surgeons appeared to have lower rates of complication, older people should be treated by more experienced surgeons.

An association between lower SES and poorer survival has been observed previously,[327, 349, 350] with one study also showing that lower SES was associated with reduced likelihood of adjuvant chemotherapy treatment.[327] Of all the potential mediators we considered, adjustment for chemotherapy treatment produced the greatest attenuation of the association between area-level SES and one-year mortality. However, the reduction was modest and the association remained statistically significant. Regardless, it is concerning that patients living in the most disadvantaged areas appeared to be less likely to see a medical oncologist, and potential differences in treatment access should be investigated further.

Consistent with some,[133, 138, 336] but not all[114, 135, 351, 352] studies, we found that higher surgeon volume was associated with lower short-term mortality, including after adjustments for age and chemotherapy treatment. The magnitude of association estimated from our propensity score-adjusted model was similar to that obtained from a propensity-matched case-control analysis of 30-day mortality among patients undergoing a pancreatic resection for any cause (< 5 versus ≥ 5 resections/year: AOR 2.04, 95% CI 1.20-3.57).[133] In two studies that had a greater separation between LV and HV categories,[138, 336] a stronger association was estimated; it remained statistically significant after adjustment for hospital volume suggesting that a substantial proportion of the apparent protective effect of hospital volume was attributable to surgeon volume. In contrast, surgeon volume was not statistically significant after accounting for hospital volume in another analysis,[352] and a protective effect of hospital volume might explain null results from studies using data from a single HV hospital.[135, 351]

Higher rates of complications may explain, in part, the higher mortality and lower survival amongst patients operated on by a LV surgeon. Three quarters of the patients who died within 90 days were operated on by a LV surgeon, and the higher proportion of deaths from surgical complications

associated with LV surgeons was statistically significant. The attenuation of the association between surgeon volume and OS with time from surgery is consistent with complications mediating the relationship. Further, we found that patients who had complications fared worse in the first 8 months following surgery, and complications have been shown previously to increase the odds of in-hospital mortality.[337]

Unlike many studies,[114, 333-335] we did not observe poorer outcomes at LV hospitals, and it may be that more complicated cases are appropriately referred to HV hospitals. Indeed, HV hospitals treated proportionally more stage II/III cases than LV hospitals. Other explanations for our null findings should be considered. Most analyses of hospital volume have used a HV threshold considerably higher than ≥ 6 resections/year.[114, 333-335] Only 5 of 50 hospitals in our study performed ≥ 11 resections/year, the minimum volume recommended by the Leapfrog Group.[353] It is possible that hospitals that were nominally HV in our analysis may not have had sufficiently high volumes for any protective effect to be apparent, although we explored a range of different thresholds and found no evidence of any association.

At the time this study was performed, gemcitabine was the standard chemotherapeutic agent used in the adjuvant setting in NSW and QLD. Consistent with results from two phase III trials comparing surgery plus gemcitabine with surgery only (CONKO-001,[3] JSAP-02[354]), we found that patients who received chemotherapy had significantly prolonged RFS. All three studies reported strikingly similar estimates of median RFS (14.3 versus 6.0 [current study], 13.4 versus 6.7 [CONKO-001], and 11.4 versus 5.0 months [JSAP-2]) and hazard ratios (0.59 [current study], 0.55 [CONKO-001], 0.60 [JSAP-2]). Unlike the CONKO-001 trial, neither our study (when using a standard model) nor the JSAP-2 trial found that chemotherapy treatment significantly improved OS, although HRs were again similar across all studies (0.72 [current study], 0.76 [CONKO-001], 0.77 [JSAP-2]). While chemotherapy treatment was an important predictor of survival ≥ 10 years from diagnosis, it was acknowledged that its use might be a proxy for better post-operative course and patient performance status.[325] This may be true for our study, but results from our propensity score-adjusted models support the conclusion that adjuvant chemotherapy treatment improves outcomes.

Several study limitations deserve mention. Despite our relatively large sample size, we were only able to explore the combined effect of surgeon and hospital volume at a rudimentary level, making it difficult to tease apart the relative contribution of these factors. Further, the thresholds used to define high- and low-volume surgeons and hospitals were relatively low. Using higher thresholds resulted in too few surgeons/hospitals in the high volume category to enable statistically robust analysis while accounting for clustering; only one surgeon performed more than 10 resections for pancreatic cancer per year. However we explored a range of different thresholds and our conclusion that surgeon but

not hospital volume influenced outcomes was unaltered. Since SES was assigned based on residential location, some individuals may be incorrectly classified. Despite careful adjustment, patient case mix might bias our estimates of associations with health service factors. To try to reduce this possibility, we adjusted for adjuvant chemotherapy treatment, in addition to comorbidities, when analysing surgical volume, mortality and survival, since it might be regarded as a surrogate for patients' "fitness". We did not capture total lymph node positivity ratio so were unable to adjust for this in our analyses.

The key strengths of this study are the relatively large sample size and the population-based design with patient records obtained for 96% of eligible patients.[339] The use of extended Cox models permitted a rich assessment of patient outcomes as time from surgery elapsed, and comprehensive data collection allowed examination of possible mediators.

Unlike some other studies we did not find any association with hospital volume, suggesting that rather than advocating a specific volume cut point guidelines may need to consider a more nuanced approach to advising on patient pathways, depending on the complexity of their disease. We did demonstrate worse survival for patients operated on by LV surgeons from the perioperative period to 1.5 years following surgery, which may be partially explained by higher rates of complications. Systems should be implemented to ensure that surgeons are completing a sufficient number of resections to optimize patient outcomes. These findings may be particularly relevant for countries with a relatively small and geographically dispersed population.

Supplementary tables

Table 9-13: Associations between selected exposure variables and aborted resection surgery: logistic regression[a].

Exposure variable	N (%)[b] All (n=365)	N (%)[b] Aborted (n=87)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[c]
Age at diagnosis, years				
<60	104 (28)	25 (29)	1	1
60-69	133 (36)	32 (37)	1.00 (0.55, 1.82)	1.00 (0.55, 1.82)
≥70	128 (35)	30 (34)	0.97 (0.53, 1.78)	0.97 (0.53, 1.78)
p-value			0.99	0.99
Socioeconomic status - quintiles				
Most disadvantaged	74 (20)	12 (14)	1	1
Second	81 (22)	21 (24)	1.81 (0.82, 4.00)	1.81 (0.82, 4.00)
Third	67 (18)	20 (23)	2.20 (0.98, 4.94)	2.20 (0.98, 4.94)
Fourth	75 (21)	20 (23)	1.88 (0.84, 4.19)	1.88 (0.84, 4.19)
Least disadvantaged	66 (18)	13 (15)	1.27 (0.53, 3.01)	1.27 (0.53, 3.01)
p-value			0.31	0.31
Place of residence				
Major City	258 (71)	59 (69)	1	1
Inner Regional	73 (20)	20 (23)	1.27 (0.71, 2.30)	1.27 (0.67, 2.42)
Outer regional/remote[d]	32 (9)	7 (8)	0.94 (0.39, 2.29)	0.95 (0.38, 2.37)
p-value			0.70	0.73
Tumour site				
Head/Neck/Uncinate process	297 (83)	73 (86)	1	1
Body/Tail	60 (17)	12 (14)	0.77 (0.39, 1.52)	0.77 (0.39, 1.52)
p-value			0.45	0.45
Preoperative assumed tumour status				
Confined to pancreas	148 (43)	28 (35)	1	1
Locally advanced	199 (57)	53 (65)	1.56 (0.93, 2.61)	1.75 (1.02, 2.99)
p-value			0.09	0.04
Any laparoscopy				
No	249 (68)	68 (78)	1	1
Yes	116 (32)	19 (22)	0.52 (0.30, 0.92)	0.51 (0.29, 0.91)
p-value			0.02	0.02
Any MRCP or CT (pancreas protocol)				
No	142 (39)	35 (40)	1	1
Yes	223 (61)	52 (60)	0.93 (0.57, 1.52)	0.90 (0.55, 1.48)
p-value			0.77	0.68
Any EUS or ERCP				
No	99 (27)	19 (22)	1	1
Yes	266 (73)	68 (78)	1.45 (0.82, 2.56)	1.49 (0.83, 2.68)
p-value			0.21	0.18
Hospital type				
Public	226 (62)	55 (63)	1	1
Private	139 (38)	32 (37)	0.93 (0.56, 1.53)	0.91 (0.54, 1.54)
p-value			0.77	0.73

Exposure variable	N (%)[b] All (n=365)	Aborted (n=87)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[c]
Surgeon volume, resections/year				
≥ 4	193 (53)	41 (48)	1	1
< 4	171 (47)	45 (52)	1.24 (0.66, 2.30)	1.17 (0.62, 2.21)
p-value			0.50	0.62
Hospital volume, resections/year				
≥ 6	245 (67)	53 (61)	1	1
< 6	120 (33)	34 (39)	1.56 (0.86, 2.81)	1.57 (0.88, 2.82)
p-value			0.14	0.13

[a] When analysing associations with hospital and surgeon volume, we adjusted for patient clustering using GEEs with an exchangeable correlation matrix.
[b] Column percentages.
[c]Adjustment variables: **Age, Socio-economic status, Tumour site** – none; **Place of residence** – age at diagnosis and SES; **Preoperative assumed tumour status** –any laparoscopy, any MRCP or CT (pancreas protocol), and any EUS or ERCP; **Any laparoscopy** – Charlson comorbidity index, any MRCP or CT (pancreas protocol), any EUS or ERCP, and hospital volume; **Any MRCP or CT (pancreas protocol), Any EUS or ERCP** – age at diagnosis, Charlson comorbidity index and hospital volume; **Hospital type, Surgeon volume –** SES; **Hospital volume** – age at diagnosis and Charlson comorbidity index.
[d] Includes very remote locations.
CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; GEE, generalised estimating equation; MRCP, magnetic resonance cholangiopancreatography; SES, socioeconomic status.

Table 9-14: Associations between selected exposure variables and recurrence-free survival[a] (n=261)[b]: Cox proportional hazards and stratified Cox models[c].

Exposure variable	N (%)	Median (months)	Crude HR (95% CI)	Adjusted HR (95% CI) [d]
Age at diagnosis, years				
<60	76 (29)	14.1	1[e]	1[e]
60-69	98 (38)	11.8	1.10 (0.76, 1.61)	1.10 (0.76, 1.61)
≥70	87 (33)	14.0	1.01 (0.68, 1.51)	1.01 (0.68, 1.51)
p-value, p-trend			0.85, 0.95	0.85, 0.95
Socioeconomic status - quintiles				
Most disadvantaged	54 (21)	8.8	1	1
Second	59 (23)	19.0	0.74 (0.46, 1.17)	0.74 (0.46, 1.17)
Third	45 (17)	12.9	0.78 (0.47, 1.28)	0.78 (0.47, 1.28)
Fourth	53 (20)	23.2	0.67 (0.41, 1.10)	0.67 (0.41, 1.10)
Least disadvantaged	49 (19)	11.7	0.94 (0.58, 1.50)	0.94 (0.58, 1.50)
p-value, p-trend			0.46, 0.68	0.46, 0.68
Place of residence				
Major City	185 (71)	13.1	1	1
Inner Regional	51 (20)	14.0	1.10 (0.75, 1.61)	1.08 (0.73, 1.59)
Outer regional/remote/very remote	24 (9)	11.1	1.15 (0.68, 1.94)	1.12 (0.65, 1.94)
p-value			0.82	0.87
Charlson comorbidity index (score)				
Low (0)	134 (52)	13.0	1	1
Medium (1)	77 (30)	19.0	0.82 (0.57, 1.18)	0.79 (0.54, 1.18)
High (≥ 2)	48 (19)	9.4	1.22 (0.81, 1.83)	1.18 (0.77, 1.81)
p-value			0.23	0.25
ECOG performance status				
Fully active	138 (60)	21.6	1	1
Not fully active	93 (40)	10.5	1.48 (1.06, 2.06)	1.50 (1.08, 2.10)
p-value			0.02	0.02
TNM stage [g]				
I	34 (13)	22.1[f]	1	1
II/III	222 (87)	11.9	1.81 (1.06, 3.08)	1.81 (1.06, 3.08)
p-value			0.03	0.03
Positive lymph nodes				
No	87 (34)	23.5[f]	1	1
Yes	170 (66)	10.5	2.19 (1.52, 3.16)	2.19 (1.52, 3.16)
p-value			<0.0001	<0.0001
Poorly differentiated / undifferentiated tumour				
No	82 (63)	13.9	1	1
Yes	49 (37)	9.0	1.34 (0.87, 2.06)	1.34 (0.87, 2.06)
p-value			0.18	0.18
Tumour site				
Head/Neck/Uncinate process	209 (82)	12.3	1	1
Body/Tail	46 (18)	17.6	0.82 (0.54, 1.25)	0.82 (0.54, 1.25)
p-value			0.35	0.35
Hospital type				
Public	156 (60)	12.5	1	1
Private	105 (40)	14.0	0.99 (0.72, 1.35)	1.05 (0.74, 1.48)
p-value			0.94	0.79
Any complication within 30 days of surgery				
No	141 (55)	14.3	1	1
Yes	116 (45)	11.7	1.18 (0.86, 1.61)	1.15 (0.84, 1.58)
p-value			0.31	0.38

Exposure variable	N (%)	Median (months)	Crude HR (95% CI)	Adjusted HR (95% CI) [d]
Margin status [h]				
Involved or clear < 1 mm	141 (56)	10.6	1	1
Clear ≥ 1 mm	112 (44)	24.0	0.63 (0.46, 0.88)	0.62 (0.45, 0.86)
p-value			0.01	0.005
Treated with adjuvant chemotherapy				
No	57 (24)	6.0	1[e]	1[e]
Yes	177 (76)	14.3	0.52 (0.36, 0.74)	0.59 (0.39, 0.88)
p-value			0.0003	0.01
Surgeon volume, resections/year				
≥ 4	142 (54)	13.0	1[e]	1
< 4	119 (46)	13.1	1.04 (0.80, 1.35)	1.09 (0.82, 1.45)
p-value			0.77	0.54
Hospital volume, resections/year				
≥ 6	178 (68)	12.1	1	1
< 6	83 (32)	19.0	0.76 (0.54, 1.09)	0.71 (0.49, 1.04)
p-value			0.13	0.08
Combined surgeon and hospital volumes, resections/year				
≥ 4 and ≥ 6 (both high)	129 (49)	13.1	1	1
≥ 4 and < 6	13 (5)	12.5	0.85 (0.34, 2.13)	0.51 (0.15, 1.76)
< 4 and ≥ 6	49 (19)	9.8	1.37 (0.92, 2.04)	1.37 (0.89, 2.11)
< 4 and < 6 (both low)	70 (27)	19.0	0.83 (0.58, 1.18)	0.84 (0.59, 1.20)
p-value			0.22	0.11

[a] Median recurrence-free survival calculated using Kaplan-Meier methods.
[b] Restricted to patients who had a completed resection, who were not found to have distant metastases during surgery, and who did not die during their acute admission.
[c] Crude hazard ratios (HRs) calculated using Cox proportional hazards (PH) models. Adjusted HRs calculated using Cox PH or stratified Cox models. When analysing associations with hospital and surgeon volume, we adjusted for patient clustering using robust sandwich estimates of standard errors.
[d] Adjustment variables: **Age, Socio-economic status, TNM stage, Positive lymph nodes, Poorly differentiated / undifferentiated tumour, Tumour site** – none; **Place of residence** – age at diagnosis, Charlson comorbidity index and adjuvant chemotherapy treatment; **Charlson comorbidity index** – age at diagnosis and socio-economic status; **ECOG performance status** – age at diagnosis and Charlson comorbidity index; **Hospital type** – age at diagnosis, Charlson comorbidity index, ECOG performance status, TNM stage and hospital volume; **Any complication** – surgeon volume and hospital volume; **Margin status** – age at diagnosis, Charlson comorbidity index, ECOG performance status and TNM stage; **Treated with adjuvant chemotherapy** – age at diagnosis, Charlson comorbidity index, ECOG performance status, TNM stage, any complication within 30 days of surgery and total length of stay; **Surgeon volume, Hospital volume, Combined surgeon and hospital volumes** – age at diagnosis, Charlson comorbidity index, ECOG performance status, TNM stage and adjuvant chemotherapy treatment.
[e] PH assumption violated for exposure variable.
[f] Median value not available due to censoring; mean survival given instead.
[g] Only 3 people had a TNM stage III tumour.
[h] "Clear margins, distance not stated" assumed to be clear ≥1 mm.
ECOG, Eastern Cooperative Oncology Group; TNM, tumour node metastases.

9.10. APPENDIX I

9.10.1. Co-author permission statement

I provide permission for these publications to be included in the thesis of Elizabeth Burmeister:

1. **Burmeister EA,** O'Connell DL, Beesley VL, Goldstein D, Gooden HM, Janda M, Jordan SJ, Merrett ND, Payne ME, Wyld D, Neale RE. Describing Patterns of Care in Pancreatic Cancer – a population-based study. Pancreas 2015; 44 (8):1259-65.
2. **EA Burmeister**, SJ Jordan, DL O'Connell, VL Beesley, D Goldstein, HM Gooden, M Janda, ND Merrett, D Wyld, RE Neale for The Pancreatic Cancer Clinical Working Group. Using a Delphi process to determine optimal care for patients with pancreatic cancer. Asia Pac J Clin Oncol 2016; 12 (2): 105-14.
3. **EA Burmeister**, M Waterhouse, SJ Jordan , DL O'Connell, ND Merrett, D Goldstein, D Wyld, V Beesley, H Gooden, M Janda, RE Neale. Determinants of survival and attempted resection in patients with non-metastatic pancreatic cancer: an Australian population-based study. Pancreatology 2016; 16 (5): 873-881.
4. **Burmeister EA**, O'Connell DL, Jordan SJ, Goldstein D, Merrett ND, Wyld D, Beesley VL, Gooden HG, Janda M, Neale RE. Factors associated with quality of care in patients with pancreatic cancer. To be published Nov 2016, MJA; 10 (25): doi: 10.5694/mja16.00567.

Name	**Signature**
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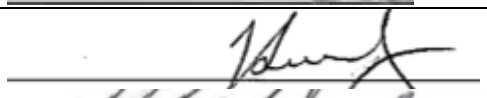
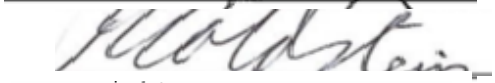
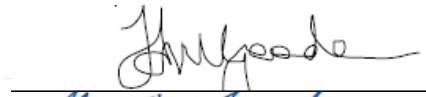
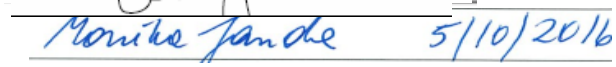
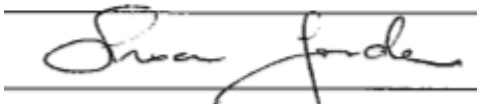
Vanessa Beesley	
David Goldstein	
Helen M. Gooden	
Monika Janda	
Susan J. Jordan	
Neil D. Merrett	
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